CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22251
Priority or Standard	Standard
Submit Date(s)	July 18, 2014
Received Date(s)	July 18, 2014
PDUFA Goal Date	May 18, 2014
Division / Office	ODE 1/ DPP
Reviewer Name(s)	Francis E. Becker, M.D.
Review Completion Date	February 12, 2015
Established Name	Lamotrigene
Trade Name	Lamictal
Therapeutic Class	Anti-epileptic
Applicant	GlaxoSmithKline LLC
Formulation(s)	Chewable Dispersible (CD) tablets: 25 mg, 50 mg, 100 mg
Dosing Regimen	25 mg up to 400 mg daily
Indication(s)	Maintenance treatment of Bipolar I Disorder

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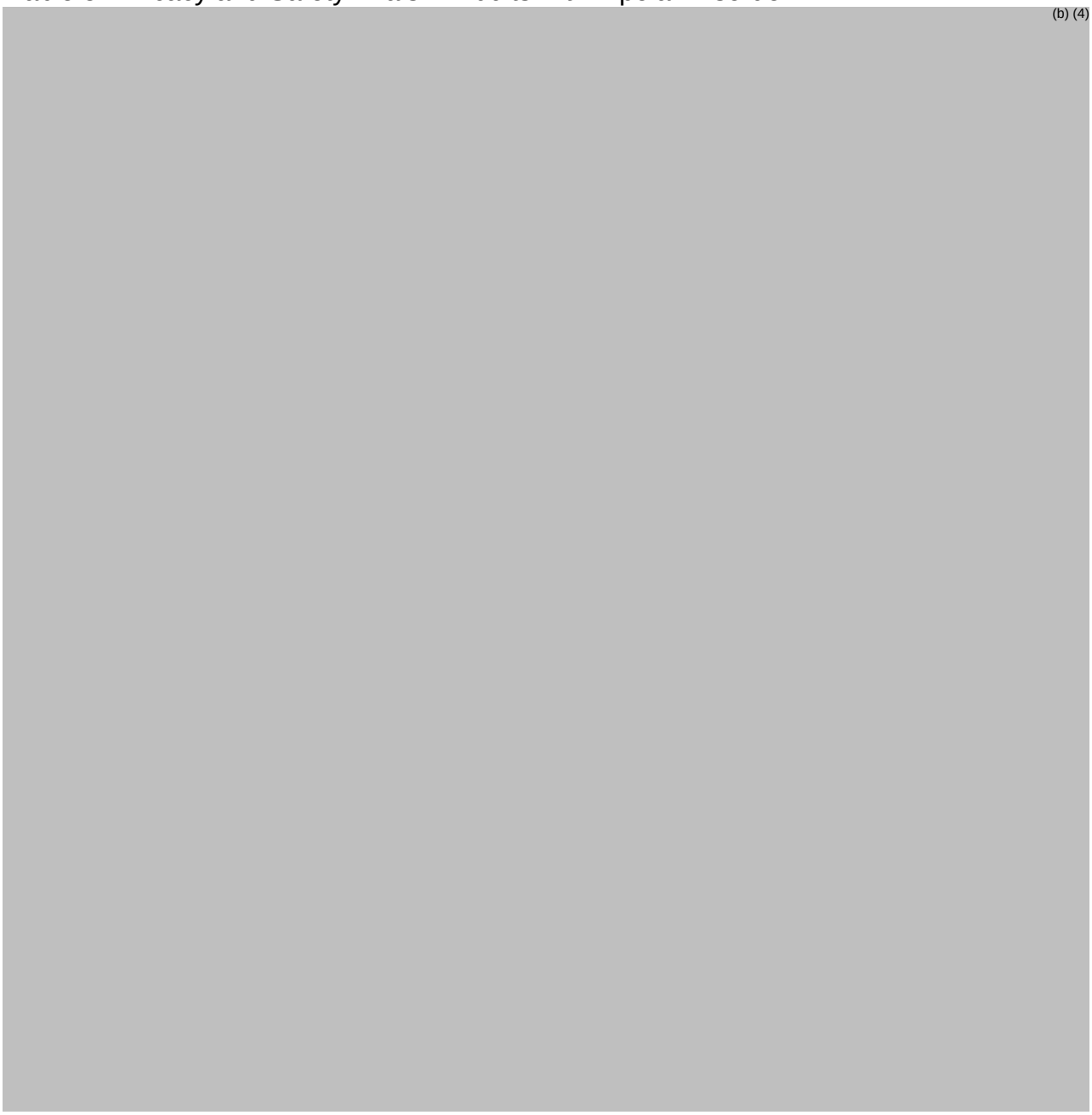

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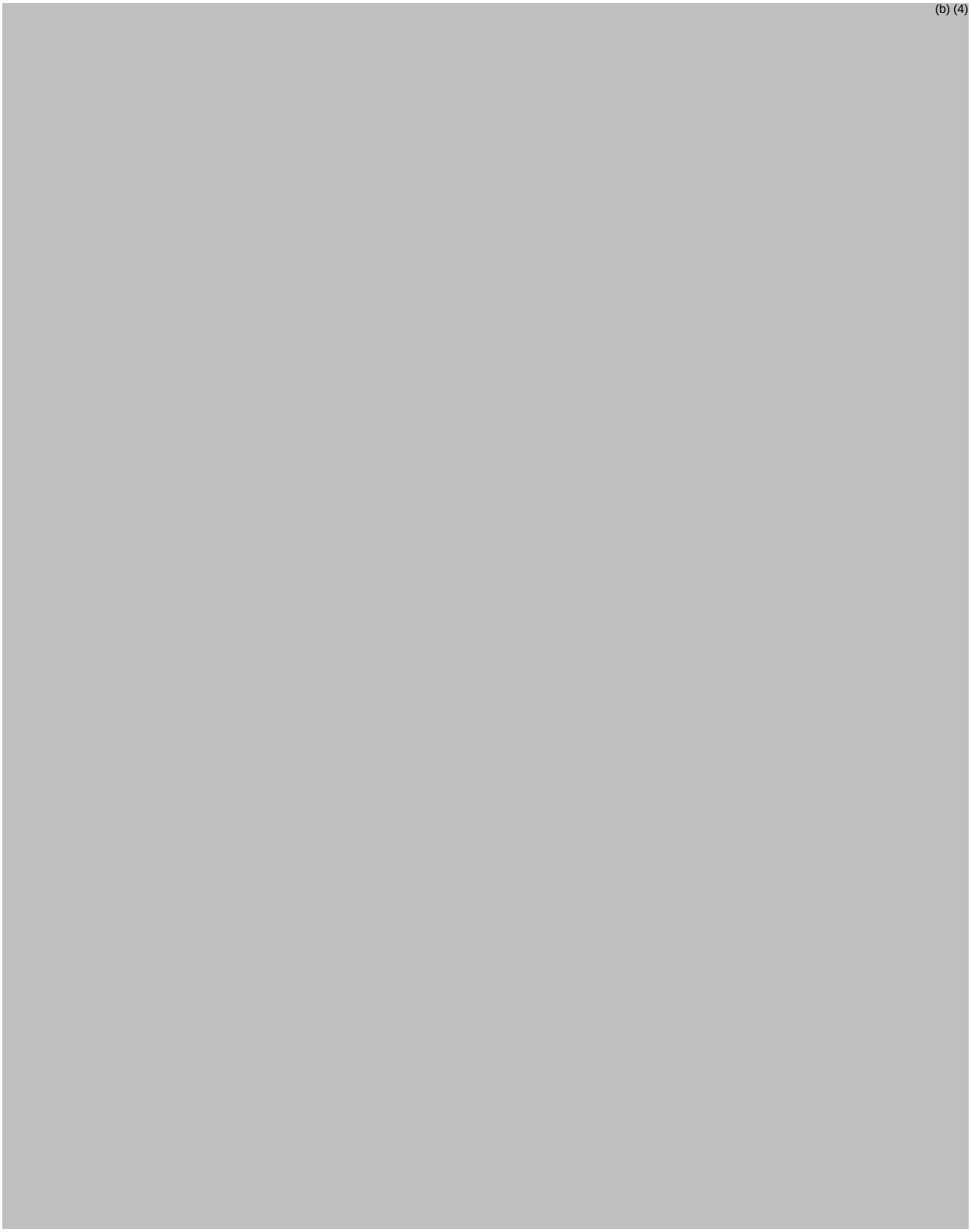

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1 Recommendations/Risk Benefit Assessment

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Trial **SCA102833** appears to be adequate for fulfillment of the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). If the sponsor wishes to pursue an indication for Lamictal in the maintenance treatment of Bipolar I Disorder in adolescents (age 13-17 years), I recommend that the sponsor conduct a trial of similar design to Trial **SCA102833** for the study population of adolescents: an outpatient, multicenter, parallel group, placebo-controlled, double-blind, randomized withdrawal trial of Lamictal in male and female adolescents, 13 to 17 years of age, diagnosed with bipolar I disorder.

1.2 Risk Benefit Assessment

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(b) (4) No new or unexpected safety signals emerged from Trial **SCA102833**. In the Randomized Phase of the trial, adverse events which occurred in at least 5% of subjects taking Lamictal and which were more common compared to patients taking placebo were influenza, oropharyngeal pain, insomnia, cough, nasopharyngitis, vomiting, contact dermatitis, upper abdominal pain and suicidal ideation. There were no deaths in Trial **SCA102833**.

In Trial **SCA102833**, the observed frequency in the Randomized Phase of possible suicide-related adverse events (PSRAEs) for Lamictal compared to placebo (7% vs. 1%, respectively) was higher than that observed in a pooled analysis of adult BPD studies (2.4% vs. 1.8%, respectively). For Trial **SCA102833**, the prospectively measured C-SSRS scores were similar for both treatment groups (11% in the LTG group and 7% in the PBO group). The results are consistent with the increased risk of suicidal ideation and behavior observed in patients taking AEDs. Suicidal ideation warnings and precautions, as well as guidance for management are provided in the current labeling.

(b) (4) the efficacy of Lamictal in the maintenance treatment of (b) (4) adolescents with BPD has not been conclusively established, based on the results of Trial **SCA102833**. (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

(b) (4) I have no recommendations for postmarket risk evaluation and mitigation strategies at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

I have no recommendations for postmarket requirements and commitments (b) (4)

2 Introduction and Regulatory Background

This supplemental New Drug Application is submitted by GlaxoSmithKline LLC in fulfillment of the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). (b) (4)

2.1 Product Information

Lamotrigine (Lamictal [LTG]; 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine) is a phenyltriazine. It is an antiepileptic drug (AED) but is chemically unrelated to other AEDs. LTG is a sodium channel blocker and a glutamate release inhibitor and was first approved on November 5 1990 in Ireland for adjunctive treatment of partial seizures in adults. It is currently approved in the United States (US), all European Union Member State countries, and Japan as well as over 70 other countries.

Lamictal is indicated for: 1) adjunctive therapy in patients 2 years and older with partial seizures, primary generalized tonic-clonic seizures, or generalized seizures of Lennox-Gastaut syndrome; 2) monotherapy in patients 16 years and older with epilepsy; and 3) maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients 18 years and older treated for acute mood episodes with standard therapy.

Lamictal contains Boxed Warning for serious skin rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and/or rash-related death. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include: 1) coadministration with valproate; 2) exceeding recommended initial dosage of Lamictal; and 3) exceeding recommended dose escalation of Lamictal. Other Warnings and Precautions in Lamictal labeling include: 1) fatal or life-threatening hypersensitivity reaction (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]); 2) blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia); 3)

suicidal behavior and ideation; 4) aseptic meningitis; and 5) medication errors involving confusion of the names Lamictal and lamotrigine with the names of other commonly used medications. In adult epilepsy studies, the most common adverse events (incidence ≥10%) were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children in epilepsy clinical studies included vomiting, infection, fever, accidental injury, pharyngitis, abdominal pain, and tremor. In adult bipolar clinical studies, the most common adverse reactions (incidence >5%) were nausea, somnolence, back pain, fatigue, rash, rhinitis, abdominal pain, and xerostomia.

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2.2 Tables of Currently Available Treatments (b) (4)

Mood stabilizers (e.g., lithium) and atypical antipsychotic medications have been used for the treatment of bipolar disorder in children and adolescents. Lithium is usually regarded as the first choice to treat bipolar disorder and is FDA-approved for the maintenance treatment of bipolar disorder in children age 12 and older. The atypical antipsychotics risperidone, aripiprazole, quetiapine, and olanzapine are approved for acute treatment of mania/hypomania in children and adolescents. These atypical antipsychotics have not been specifically studied in long-term pediatric maintenance trials. However, they are generally used for maintenance treatment based on extrapolation of data from the short-term efficacy trials. The anticonvulsant medications (lamotrigine and valproate) are currently not approved for the treatment of bipolar disorder in children. FDA-approved treatments for bipolar disorder in children are shown in the **Table 1** below.

Table 1: FDA-Approved Pediatric and Adolescent Bipolar Treatment Regimens

Product Name	Trade Name	FDA-Approved Pediatric Indication			FDA-Approved Pediatric Age Group
		Manic	Mixed	Maintenance	
Mood Stabilizers					
Lithium		X		X	12-17 years
Atypical Antipsychotics					
Aripiprazole	Abilify	X	X		13-17 years
Olanzapine	Zyprexa	X		X	13-17 years
Quetiapine	Seroquel	X			10-17 years
Risperidone	Risperdal	X			10-17 years

2.3 Availability of (b) (4) Active Ingredient in the United States

LTG is available in the United States as Lamictal (lamotrigine) Tablets, LTG (lamotrigine) Chewable Dispersible Tablets (CD), and LTG (lamotrigine) Orally Disintegrating Tablets (ODT). LTG (lamotrigine) Tablets were initially approved by the Food and Drug Administration (FDA) in the US in 1994 as adjunctive treatment of partial seizures in adults. Subsequently, LTG was approved for adjunctive treatment of the generalized seizures of Lennox-Gastaut syndrome in pediatric (2-16 years of age) and adult subjects (August 1998), and for conversion to monotherapy in adults receiving therapy with a single enzyme-inducing antiepileptic drug (AED) (December 1998). In January 2003, LTG was approved for adjunctive treatment for partial seizures in pediatric subjects (2-16 years of age), and in January 2004 for conversion to monotherapy from valproate (VPA) in adult subjects with partial seizures. More recently, Lamictal was approved as adjunctive treatment of primary generalized tonic-clonic seizures in patients 2 years of age and older (September 2006). Finally, Lamictal ODT Orally Disintegrating Tablets were approved in May 2009 based on demonstration of bioequivalence to LTG Tablets.

Lamictal was approved by the US FDA in June 2003 (New Drug Application [NDA] 020241 S-017 Tablets, NDA 020764 S-011 Chewable Dispersible Tablets) for the delay of mood episodes (depression, mania, hypomania, mixed episodes) in adult patients with bipolar I disorder (BPD).

2.4 Important Safety Issues With Consideration to Related Drugs

In addition to Lamictal (lamotrigine), the anticonvulsant medications include Depakote/Depakene (divalproex sodium, valproic acid, or valproate sodium,), Tegretol (carbamazepine), Neurontin (gabapentin), Lyrica (pregabalin), and Topamax (topiramate). Lamictal is the only anticonvulsant medication that carries an indication for maintenance treatment of Bipolar I Disorder in adults. Depakote carries an indication for

treatment of manic episodes associated with bipolar disorder. However, age range is not specified in Depakote labeling, and there is no information about pediatric studies.

All of these anticonvulsant medications contain warnings in labeling regarding the risk of suicidal behavior and ideation. Some of the anticonvulsants (Depakote, Lyrica, Neurontin, and Tegretol) also have warnings regarding risk of angioedema and/or hypersensitivity reactions (hives, dyspnea, wheezing). In addition, there are warnings in some of the anticonvulsants for hematologic abnormalities: patients taking Tegretol are at risk for aplastic anemia and agranulocytosis, while patients taking Depakote are at risk for thrombocytopenia. Serious dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) have been reported during treatment with Tegretol. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has also occurred with Tegretol. Other warnings described in labeling include hepatotoxicity (Depakote), pancreatitis (Depakote), hypothermia (Depakote, Topamax), mood or thought disorders (Lyrica, Neurontin, Topamax), and AV heart block (Tegretol). Overall, common adverse events include dizziness, somnolence, blurred vision or diplopia, abdominal pain, and changes in weight.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Discussions with the sponsor regarding a pediatric study of lamotrigine (LTG) began on February 1, 2001 at a Pre-sNDA meeting for LTG tablets (**NDA 20241**) and CD tablets (**NDA 20764**) in the treatment of adult bipolar I disorder. At that time, FDA granted a waiver for a pediatric assessment in patients less than 13 years of age and a deferral for patients 13 to 17 years of age. The sponsor agreed to conduct a deferred study.

The sNDAs for LTG tablets (**NDA 20241**) and CD tablets (**NDA 20764**) were submitted on June 5, 2002 and were approved on June 20, 2003, as maintenance treatment of bipolar I disorder in patients ≥ 18 years of age treated for acute mood episodes with standard therapy. In the approval letter, the FDA did not require a pediatric assessment as a formal post-marketing commitment because the FDA Pediatric Rule was being challenged in court at the time. Subsequently, a legislative requirement for pediatric studies of approved medicines was formalized via the Pediatric Research Equity Act (PREA) of 2007.

In December 2004 the sponsor initiated interactions with the Division of Psychiatry Products (DPP) with the submission of concept protocol **SCA 102833**, which was designed to investigate maintenance treatment of pediatric bipolar disorder (**IND 049916**). In correspondence with the sponsor dated July 7, 2007, FDA agreed with the elements of the proposed protocol, (b) (4) Key discussions with DPP were around the primary endpoint and the study population age range:

- The sponsor and DPP reached agreement that the primary endpoint for the study would be Time to Occurrence of a Bipolar Event (TOBE), even though the sponsor's adult bipolar studies used a primary analysis based on the endpoint Time to Intervention for a Mood Episode (TIME).
- In June 2007, DPP agreed to the sponsor's proposal to include only adolescents aged 13-17, a post-pubescent population where it is accepted that the presentation is similar to the clinical presentation in adults. However, in October 2007, DPP requested that children and adolescents be included. The sponsor agreed to extend the age group to 10 years of age. In the reporting and analysis plan (RAP) subgroup analyses were prespecified including subgroup analysis by age groups (10-12 years old and 13-17 years old).

The sponsor was also developing an ODT formulation of LTG to be bioequivalent to the approved immediate release formulations. At a Pre-NDA Meeting on October 1, 2007 with the sponsor and representatives of the Division of Neurology Products (DNP) and DPP, it was agreed that the single trial **SCA102833** would satisfy the PREA requirements for the ODT formulation as well. The new protocol was submitted to **IND 049916** on July 8, 2008 and the first subject was enrolled on July 31, 2008.

The **NDA 22251** for LTG ODT and the associated labeling supplements for LTG tablets (**NDA 20241**) and CD tablets (**NDA 20764**) were approved on May 8, 2009. At that time, the Agency formally waived the requirement for a pediatric assessment in children below the age of 10 years with bipolar disorder and established the PMR noted above for the three bioequivalent products.

2.6 Other Relevant Background Information

In this submission, no other relevant information, such as important regulatory actions in other countries or important information contained in foreign labeling, is included.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of this submission is acceptable.

3.2 Compliance with Good Clinical Practices

It appears that the clinical trial was conducted in compliance with good clinical practice. The sponsor obtained approval from the appropriate regulatory agency to conduct the trial in accordance with applicable country-specific regulatory requirements. In addition, the trial was conducted in accordance with Good Clinical Practice (GCP), all applicable

subject privacy requirements, and the guiding principles of the declaration of Helsinki, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments.
- Subject informed consent/assent.
- Investigator reporting requirements.

3.3 Financial Disclosures

The sponsor has provided documentation certifying that each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor. There does not appear to be any instances of conflict of interest which affected the conduct or results of the trials. Please see the Clinical Investigator Financial Disclosure below:

Table 2: Clinical Investigator Financial Disclosure

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 258		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N.A. Significant payments of other sorts: N.A. Proprietary interest in the product tested held by investigator: N.A. Significant equity interest held by investigator in sponsor of covered study: N.A.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N.A	No ☐ (Request details from applicant).
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N.A	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ N.A	No ☐ (Request explanation from applicant)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Biostatistics

The final report from the Office of Biostatistics is pending at the time of this writing. However, I have discussed the sNDA with the Biostatistics Reviewer, Fanhui Kong, who has reached preliminary conclusions that in Trial **SCA102833**, statistical significance for

Lamictal compared to placebo was not achieved for the primary efficacy endpoint, time to occurrence of a bipolar event (TOBE), in male and female children and adolescents, 10 to 17 years of age, diagnosed with bipolar I disorder. (b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Trial **SCA102833** is the only efficacy trial conducted in children and adolescents with Bipolar Disorder (BPD) and is the focus of this sNDA. Per previous agreement with the FDA, data from the 2 pivotal trials in adults with BPD (Trials **SACB2003** and **SCAB2006**) and the 2 controlled trials of adjunctive treatment with Lamictal in pediatric patients with epilepsy (**UK123** and **US40**) are also presented for comparison, as shown in **Table 3**, **Table 4**, and **Table 5** below.

Table 3: Efficacy and Safety Trials in Children and Adolescents with Bipolar Disorder

Trial Number	**Trial Design**	**Drugs/Dose/Duration**	**Number and Type of Subjects**	**Trial Status**
SCA102833	Multicenter (32 centers in US), placebo-controlled, double-blind, randomized withdrawal trial of lamotrigine (LTG) in male and female children and adolescents, 10 to 17 years of age, diagnosed with bipolar I disorder.	LTG 5mg, 25mg, and 100 mg chewable dispersible (CD) tablets, with dose escalation based on subject's bipolar medication, age, and weight: 18-week Open-label phase (plus up to 4 week taper) LTG 25mg and 100mg and Placebo to match 36-week double-blind, randomized phase (plus up to 4 week taper)	LTG: 301 subjects open-label (298 ITT population) LTG: 87 randomized/24 completed Placebo: 86 randomized/25 completed	Completed

Source: NDA 22521 SD-220; 5.2 Tabular Listing; Table 1, pages 1-3

Table 4: Efficacy and Safety Trials in Children and Adolescents with Seizure Disorders

Trial Number	**Trial Design**	**Drugs/Dose/Duration**	**Number and Type of Subjects**	**Trial Status**
UK 123	Randomized, double-blind, placebo-controlled, efficacy trial of LTG as adjunctive treatment of Lennox-Gastaut syndrome in subjects, 3 to 25 years of age* *Only subjects <16 were included in the ISS database	LTG 5mg, 25mg, and 100mg CD tablets, 50mg/day to 400 mg/day (after dose escalation, dependent on concomitant therapy, body weight, and seizure control); oral; 16 weeks (6-week dose escalation phase and 10-week maintenance phase (plus up to 4 week taper) Placebo oral: 16 weeks (6-week dose escalation phase and 10-week maintenance phase (plus up to 4 week taper)	140 randomized LTG: 70 randomized/64 completed Placebo: 70 randomized/60 completed	Completed (submitted as part of NDA 020764, approved August 1998)
US 40	Randomized, double-blind, placebo-controlled efficacy, safety, and PK trial in subjects 2 to 16 years of age [US] and 2 to 12 years [France] with partial seizures	LTG 5mg, 25mg, and 100mg CD tablets: 1 mg/kg/day to 15 mg/kg/day; oral; 18 weeks (6 weeks of dose escalation and 12 weeks maintenance) (plus 2 to 7 weeks taper and follow-up)	199 randomized LTG: 98 randomized/84 completed Placebo: 101 randomized/83 completed	Completed (submitted as part of NDA 020764/S-002, approved January 2003)

Source: NDA 22521 SD-220; 5.2 Tabular Listing; Table 1, pages 1-3

Table 5: Efficacy and Safety Trials in Adults with Bipolar Disorder

Trial Number	**Trial Design**	**Drugs/Dose/Duration**	**Number and Type of Subjects**	**Trial Status**
SCAB2003	Randomized, double-dummy, double-blind, placebo-controlled, fixed-dose relapse prevention trial of depression and/or mania in subjects with bipolar I disorder	Preliminary Phase (Open-label): LTG 25 mg CD tablets; 100-400mg/day depending on concomitant medication; oral; 8-16 weeks Randomized Phase: LTG 25mg and 100 mg CD tablets; 50mg/day, 200 mg/day, or 400 mg/day; oral 76 weeks Placebo tablets; oral; 76 weeks	LTG: 966 subjects open-label Randomized: LTG: 221 randomized/79 completed Placebo: 121 randomized/23 completed	Completed
SCAB2006	Randomized, double-dummy, double-blind, placebo-controlled, active-controlled, flexible-dose relapse prevention trial of depression and/or mania in subjects with bipolar I disorder	Preliminary Phase (Open-label); LTG 25 mg CD tablets100-400mg/day depending on concomitant medication; oral; 8-16 weeks Randomized Phase: LTG 100mg CD tablets; 100-400 mg/day (up to 800mg/day depending on concomitant medication); oral; 76 weeks Lithium 300mg tablets; serum 0.8-1.1mEq/L; oral; 76 weeks	LTG: 349 subjects open-label Randomized: LTG: 59 randomized/10 completed Lithium: 46 randomized/10 completed Placebo: 70 randomized/5 completed	Completed

Source: NDA 22521 SD-220; 5.2 Tabular Listing; Table 1, pages 1-3

5.2 Review Strategy

This review was conducted by analyzing the completed trials listed in the **Table 3**, **Table 4**, and **Table 5** above. However, the primary focus was on Trial **SCA102833** because this was the only efficacy trial conducted in children and adolescents with Bipolar Disorder (BPD). The other trials included in this submission (**UK 123**, **US 40**, **SCAB2003**, and **SCAB2006**) were previously reviewed during the approval process for their respective indications. Therefore, they were reviewed in the current submission for purposes of comparison of data to Trial **SCA102833**. The review included clinical summaries, integrated summary of efficacy, integrated summary of safety, and analysis of individual trials including subject data, summary tables, and raw data provided by the sponsor.

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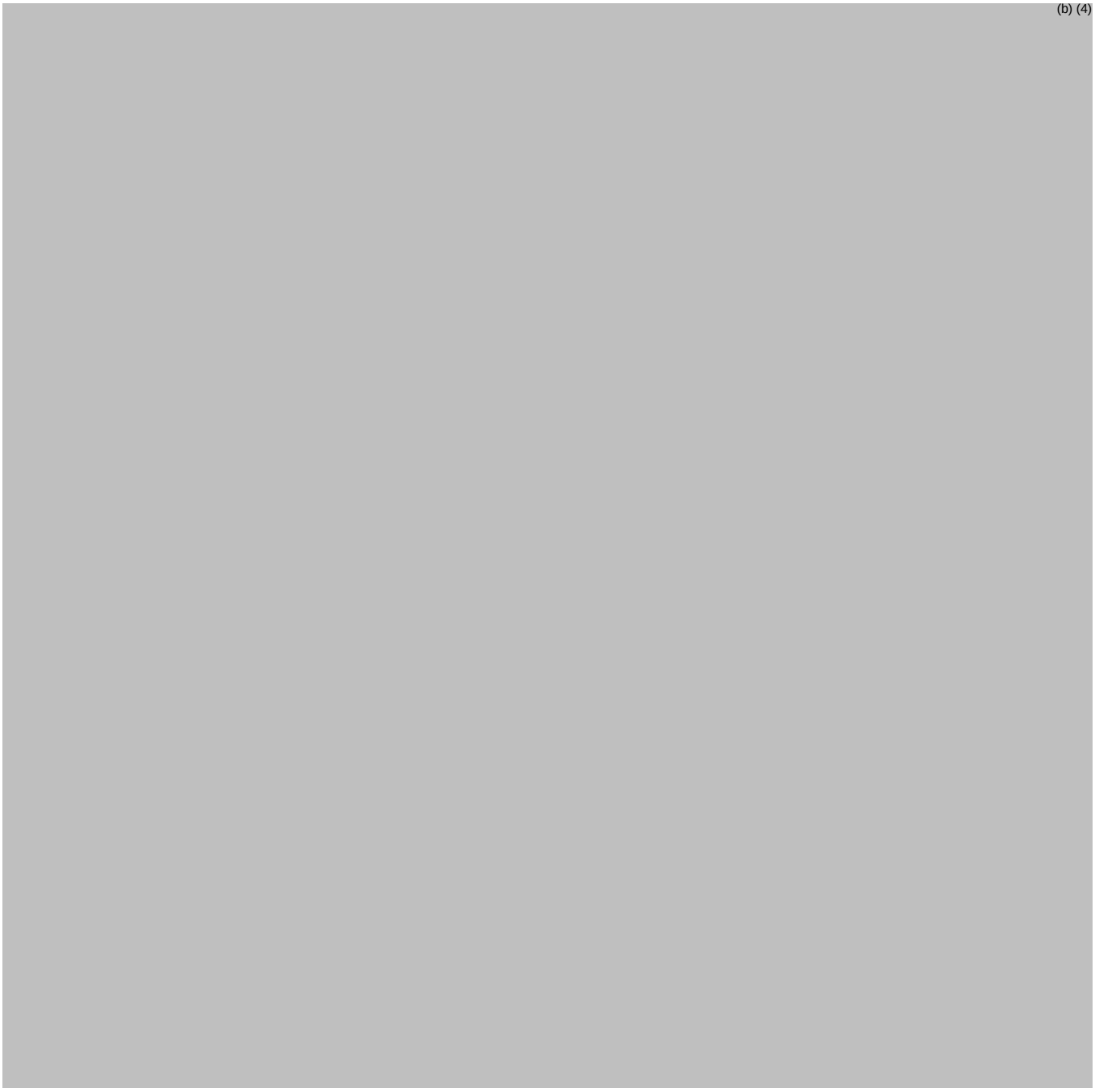

7 Review of Safety

Safety Summary

Overall, the safety profile in Trial **SCA102833** was similar to that in adults with Bipolar Disorder (BPD) and pediatric subjects with epilepsy. LTG, administered in accordance

with the dosing regimen described in the protocol, was generally well tolerated in the population studied, and the AE profile was consistent with current product labeling. No new or unexpected safety signals emerged from the laboratory analyses, vital sign evaluations, involuntary movement scales, ECG, or AE reporting. The pattern of frequencies of AEs was similar between the 10-12 year-old group and the 13-17 year-old group, and the majority of SAEs were related to the condition under study (e.g., mania, agitation). In the Randomized Phase of the trial, adverse events which occurred in at least 5% of subjects taking Lamictal (N=87) and which were more common compared to patients taking placebo (N=86) were influenza (Lamictal 8%, placebo 2%), oropharyngeal pain (Lamictal 8%, placebo 2%), insomnia (Lamictal 7%, placebo 6%), cough (Lamictal 7%, placebo 5%), nasopharyngitis (Lamictal 6%, placebo 5%), vomiting (Lamictal 6%, placebo 2%), contact dermatitis (Lamictal 5%, placebo 2%), upper abdominal pain (Lamictal 5%, placebo 1%), and suicidal ideation (Lamictal 5%, placebo 0%). There were no deaths in Trial **SCA102833**.

For the AE of special interest of rash, while there was 1 (0.3%) SAE of rash in the OL Phase of Trial **SCA102833**, no subject experienced Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). The overall rate of “all rash” was lower than that observed in previous clinical studies, although the sample is small and occurrence in the larger population remains possible.

In Trial **SCA102833**, the observed frequency in the Randomized Phase of PSRAEs for LTG compared to PBO (7% vs. 1%, respectively) was higher than that observed in a pooled analysis adult BPD studies (2.4% vs. 1.8%, respectively). During the OL Phase, 17% of subjects had an event recorded on the C-SSRS (any event, 1-10). During the Randomized Phase, the prospectively measured C-SSRS scores were similar for both treatment groups (11% in the LTG group and 7% in the PBO group). Review of individual PSRAEs in Trial **SCA102833** did not reveal consistent patterns of duration of LTG treatment, gender, age, or C-SSRS status. Caution must be exercised when looking at the results of a single trial, but the current results are consistent with the increased risk of suicidal ideation and behavior observed in patients taking AEDs. Suicidal ideation warnings and precautions, as well as guidance for management are provided in the current labeling.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The focus of my safety review was on the safety data from Trial **SCA102833**, the only efficacy trial of Lamictal conducted in children and adolescents with BPD and the focus of this sNDA. Per previous agreement with the FDA, the sponsor also submitted safety data from the 2 pivotal trials in adults with BPD (Trials **SCAB2003** and **SCAB2006**) and the 2 controlled trials of adjunctive treatment with Lamictal in pediatric patients with

epilepsy (Trials **UK123** and **US40**) for comparative purposes. The trials reviewed are listed in **Table 3**, **Table 4**, and **Table 5** in **Section 5.1** above. My safety review included review of individual study reports, figures, tables, and raw data provided by the sponsor, as well as the sponsor's Summary of Clinical Safety. While the sponsor presented safety information From Trial **SCA102833** for the entire trial population (age 10-17), discussion and comparison with adult BPD trials and pediatric epilepsy trials was focused on the 13-17 year-old population (b) (4)

7.1.2 Categorization of Adverse Events

Throughout the safety section, the sponsor presented grouped terms for mania and rash. "All Rash" included the following verbatim terms: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.

"All Mania" included the following verbatim terms: bipolar I- worsening (self-harm)-mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, and worsening manic symptoms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The study groupings are provided in **Table 53** below.

Table 53: Study Groupings

Study Grouping	Studies
Pediatric BPD Study	OL and Randomized Treatment Phases of Study SCA102833
Adult BPD Studies	Preliminary (OL) and Randomized Treatment Phases of Studies SCAB2003 and SCAB2006 (combined)
Adjunctive Pediatric Epilepsy Studies	Double-blind Treatment Phase of Studies US 40 and UK 123 (combined)

Electronically copied and reproduced from sponsor's submission: Summary of Clinical Safety, Table 2, page 8

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, the safety data was adequate for review. The Safety Population consisted of all subjects who took at least 1 dose of study drug. A summary of the composition of the safety population by study grouping is provided in Table 54 below.

Table 54: Composition of Safety Population

Study	Population	Number (%) of Subjects		
		OL Phase	Randomized Phase	
			PBO	LTG [a]
SCA102833	Intent to Treat (ITT)			
	Overall (10-17 yrs)	298	86	87
	By age group			
	10-12 yrs	117	33	33
	13-17 yrs	181	53	54
SCAB2003 & SCAB2006	Safety	1305	190	227
US 40 & UK 123	Safety	NA	171	168

NA= not applicable
Note: the ITT population was used for safety evaluations in Trial SCA102833.
Electronically copied and reproduced from sponsor's submission: Summary of Clinical Safety, Table 3, page 9

7.2.2 Explorations for Dose Response

Explorations for dose response were not specifically addressed in this sNDA. In Trial **SCA102833**, LTG dose was flexible depending on subject's age and concomitant medication.

7.2.4 Routine Clinical Testing

The types and frequency of safety assessments were appropriate (b) (4) and were adequate for determining potential safety problems.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in Trial **SCA102833**.

7.3.2 Nonfatal Serious Adverse Events

In the OL Phase of Trial **SCA102833**, 18 subjects reported a total of 22 SAEs (**Table 55** and **Table 56**). A total of 15/18 subjects were withdrawn due to SAEs. SAEs reported in more than 1 subject included suicidal ideation (2%), agitation (1%), mania (1%), and irritability (<1%), as shown in **Table 55** below.

Table 55: Summary of Serious Adverse Events (SAEs) in OL Phase (OL ITT Population)

System Organ Class Preferred Term	LTG (N=298)
Any event, n (%)	**18 (6)**
Suicidal ideation	5 (2)
All Mania*	4 (1)
-Mania	3 (1)
-Bipolar I disorder	1 (<1)
Agitation	3 (1)
Irritability	2 (<1)
Aggression	1 (<1)
Anxiety	1 (<1)
Impulsive behavior	1 (<1)
Intentional self-injury	1 (<1)
Pressure of speech	1 (<1)
Neoplasm	1 (<1)
Asthma	1 (<1)
All Rash	1 (<1)
-Rash	1 (<1)

*All Mania included the following verbatim terms: bipolar I- worsening (self-harm)- mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, worsening manic symptoms.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 47, page 113.

An event of bipolar disorder (3%) was reported as an SAE in the OL Taper Phase, as shown in **Table 56** below.

Table 56: Subjects Reporting SAEs (ITT Population, OL and OL Taper Phases)

Subject	Age/Sex/Race	Preferred Term	Withdrawn Y/N	Resolved Y/N
Open-Label Phase				
1131	17/W/F	Suicidal ideation	Y	Y
1134	17/F/B	Anxiety	Y	Y
1143	13/F/W	Suicidal ideation	Y	Y
1253	14/F/W	Bipolar I disorder Intentional self-injury	Y Y	Y Y
2879	12/M/B	Agitation Irritability Pressure of speech	Y Y Y	N N N
1012	12/M/B	Mania	Y	Y
2003	17/F/W	Impulsive behavior	N	Y
5383	16/M/B	Mania	Y	Y
1376	11/M/W	Neoplasm	Y	Y
3632	15/M/W	Mania	Y	Y
3638	11/M/B	Agitation	N	Y
1647	14/M/W	Rash	Y	Y
1654	13/M/W	Agitation Irritability	Y Y	Y Y
2751	16/F/W	Suicidal ideation	Y	Y
1752	16/F/W	Suicidal ideation	Y	Y
5880	12/F/Mx	Suicidal ideation	Y	Y
6240	12/W/M	Aggression	Y	N
5772	11/M/B	Asthma	N	Y
OL Taper Phase				
4753	16/M/W	Bipolar disorder	N	Y

W=White, B=Black, Mx=Mixed, M=Male, F=Female, N=No, Y=Yes
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 47, page 113.

Narratives of particular interest in patients who received LTG during the OL Phase and developed SAEs are as follows:

- Subject 001131 (SAE: Suicidal ideation): This 17-year-old female received lamotrigine at increasing total daily dose ranging from 25 mg to 200 mg daily during the OL Phase. Concomitant medications included aripiprazole. It was reported that the patient had shown suicidal ideation throughout the trial and in the past. On (b) (6) days after starting open-label lamotrigine, the patient was hospitalized for suicidal thought. Lamotrigine and aripiprazole were discontinued and the patient was started on Celexa. The event resolved on (b) (6) . The investigator reported that the event was possibly due to situational issues currently ongoing with the patient.

- Subject 001143 (SAE: Suicidal ideation): This 13-year-old female received oral lamotrigine at 25 mg alternate days from 1-11-12 to 1-24-12. The patient's investigational product was increased to 75 mg/day from 50 mg/day on 2-25-12. On (b) (6) days after the start of lamotrigine, the patient developed grade 1 or mild suicidal ideation relating to her having a difficult time with the loss of her father. No additional treatment was given. Treatment with lamotrigine was discontinued on 3-5-12 and the patient was withdrawn from the trial. The event resolved on (b) (6). The investigator considered that there was a reasonable possibility that the suicidal ideation resulting in hospitalization may have been caused by lamotrigine.
- Subject 001253 (SAE: Bipolar I disorder, Intentional self-injury): This 14-year-old female received lamotrigine at an increasing total daily dose ranging from 25 mg to 300 mg daily from 12-16-08. On (b) (6), the patient developed worsening of bipolar I – worsening mood state mixed and severe self-harm (cutting her arm with deep lacerations and bleeding). The patient was hospitalized. YMRS was 25, QIDS-A17-C was 17, and CGI-BP/I severity was severely ill for a, b, and c. Suicidal ideation was denied. She was reported to be enraged and irritable with labile affect. Treatment with investigational product was discontinued on 2-20-09, and the patient was withdrawn from the trial. The events resolved on (b) (6). The investigator considered this to be a severe worsening of bipolar I – mixed type disorder.
- Subject 001376 (SAE: Neoplasm): This 11-year-old male received oral lamotrigine for (b) (6) days and was then admitted to the hospital to undergo surgery to remove an ankle tumor. Treatment with lamotrigine was discontinued and the patient was withdrawn from the trial. Pathology reports suggested malignancy (awaiting further classification).
- Subject 001647 (SAE: Rash): This 15-year-old male received 25 mg oral lamotrigine on alternate days from 3-10-10 to 6-4-10. Concomitant medications included semisodium valproate and Seroquel. On (b) (6), the patient developed a severe rash (Grade 3) on chest, arms, neck, and face and was hospitalized. Treatment with lamotrigine was discontinued on 6-4-10 and the patient was withdrawn from the trial. The event resolved on (b) (6).
- Subject 001752 (SAE: Suicidal ideation): This 16-year-old female received oral lamotrigine at a dose of 25 mg on alternate days from 8-22-08 to 9-18-08, increased to 50 mg on alternate days from 9-19-08 to 9-26-08, increased to 75 mg on alternate days from 9-27-08 to 10-2-08, and increased to 100 mg from 10-3-08 to 10-9-08. From 10-10-08, the patient was receiving lamotrigine 125 mg on alternate days. Concomitant medications included semisodium valproate. On (b) (6), the patient developed moderate suicidal ideation worsening and was hospitalized. The patient reported experiencing bad memories from the emotional and verbal abuse she received from her father (parents now divorced) which were now more present due to a recent move from her home into her mother's fiancée's home. She does not believe her mother's fiancée would do anything to harm her but still struggled with this fear. The patient was hospitalized at her own

request as she reported fear of being safe. In the hospital, the patient was started on Wellbutrin 300 mg daily and Seroquel XL 25 mg QHS. Treatment with lamotrigine was discontinued on 11-12-08, and the subject was withdrawn from the trial. The subject reported that she was doing really well following hospitalization.

- Subject 002003 (SAE: Impulsive behavior): This 17-year-old female received lamotrigine at 25 mg daily from 4-8-09 to 4-13-19 (concomitant medications included lithium, Percocet, and diazepam. On (b) (6), the patient developed moderate increase in impulsive behavior and was hospitalized. The patient admitted to not taking lithium as prescribed. Treatment with lamotrigine was discontinued due to the subject being noncompliant and not due to serious event. The event resolved on (b) (6).
- Subject 002751 (SAE: Suicidal ideation): This 16-year-old female received oral lamotrigine at a total daily dose ranging from 25 mg to 300 mg from 11-5-08. On 2-2-09, the patient developed severe suicidal ideation. She made an aborted suicide attempt by almost drowning herself in the bath tub on (b) (6) and was hospitalized. Treatment with lamotrigine was discontinued on 3-4-09 and the patient was withdrawn from the trial. In 2006, the patient attempted suicide by taking “a lot of ibuprofen.” She had suicidal ideation and was cutting herself in July of 2006.
- Subject 005772 (SAE: Asthma): This 11-year-old male received oral lamotrigine at a starting dose of 10 mg from 4-2-14. Medical conditions included asthma and seasonal allergic rhinitis. Concomitant medications included aripiprazole, methylphenidate hydrochloride, Allegra D, fluticasone propionate, and ranitidine hydrochloride. On (b) (6) days after starting lamotrigine, the patient experienced symptoms of shallow breaths and audible wheezing, unresponsive to albuterol at home, and was hospitalized with moderate exacerbation of asthma. The patient was treated with prednisolone and pirbuterol acetate. Treatment with lamotrigine was continued. The event resolved on (b) (6).
- Subject 005880 SAE: Suicidal ideation): This 12-year-old female received oral lamotrigine at increasing total daily dose ranging from 5 mg to 50 mg daily starting on 4-28-12. The patient’s past history included sexual abuse. On (b) (6), the patient developed grade 2 or moderate suicidal ideation. The patient’s mother found two notes that the patient had written which expressed suicidal ideation. The patient was admitted to the hospital psychiatry ward, and the patient was withdrawn from the trial due to lack of efficacy. The patient was then prescribed non-research lamotrigine (Lamictal) 50 mg daily. The event resolved on (b) (6). The patient had previous suicidal ideation intermittent since 2010 and self-harmed in 2008. The patient had no psychosocial stressors. The patient had expressed suicidal ideation during the trial (baseline, visit 4, and visit 5). The most common ideation was “I wish I was dead” and the most severe ideation was “I want to die.”
- Subject 006240 (SAE: Aggression): This 12-year-old male received oral lamotrigine at a total daily dose of 10 mg from 3-20-12 to 7-5-12. Medical

conditions included ADHD and bipolar I disorder. Concomitant medications included methylphenidate hydrochloride. On (b) (6), the patient developed grade 3 or severe aggression and was hospitalized. Treatment with lamotrigine was discontinued on 7-5-12 and the patient was withdrawn from the trial. The event improved on an unspecified date. The investigator considered that there was a reasonable possibility that the aggression may have been caused by lamotrigine. The patient was lost to follow-up.

In the Randomized Phase, 4 subjects reported 4 SAEs (**Table 57**). Three (3%) of the subjects were in the PBO group (bipolar I disorder, mania, and intentional overdose) and 1 (1%) subject was in the LTG group (emotional disorder). The 3 subjects in the PBO group were withdrawn due to their SAEs, but the 1 subject in the LTG group was not withdrawn due to the SAE.

Table 57: Summary of Serious Adverse Events (SAEs) with Onset in Randomized Phase (ITT Population, Randomized Phase)

System Organ Class Preferred Term	PBO (N=86)	LTG (N=87)
Any event, n (%)	**3 (3)**	**1 (1)**
Emotional disorder	0	1 (1)
All Mania	2 (2)	0
-Bipolar I disorder	1 (1)	0
-Mania	1 (1)	0
Intentional overdose	1 (1)	0

All Mania included the following verbatim terms: bipolar I- worsening (self-harm)- mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, worsening manic symptoms.
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The narrative of the patient in the LTG group is as follows:

- Subject 001637 (SAE: Emotional disorder): This 13-year-old female received lamotrigine ranging from 20 mg to 300 mg daily from 7-17-09 to 12-23-09 during the open-label phase. The patient was randomized to receive lamotrigine on 12-24-09. Concomitant medications included aripiprazole. On (b) (6), the patient developed grade 2 or moderate emotional state due to difficulty dealing with alleged sexual assault and was hospitalized. Treatment with investigational product was continued. The event improved on an unspecified date. It was determined that this event was not an exacerbation of the patient's illness, and it was decided that the inpatient hospitalization was allowable per protocol and that the patient could continue participation in the trial. The patient had not missed

any doses of study medication and would continue the medication in the hospital as prescribed. Subsequently, the patient was lost to follow-up.

In the Double-blind Taper Phase, there were no SAEs reported in the LTG group. In the PBO group, 2 (3%) subjects reported 3 SAEs (infectious mononucleosis, urinary tract infection, and suicidal ideation). Neither subject was withdrawn from the trial due to these SAEs (**Table 58**).

Table 58: Subjects Reporting SAEs (ITT Population, Randomized and Double-Blind Taper Phases)

Subject	Age/Sex/Race	Preferred Term	Withdrawn Y/N	Resolved Y/N
Randomized Phase				
LTG				
1637	12/F/W	Emotional disorder	N	N
PBO				
1011	12/W/M	Mania	Y	Y
392	13/F/W	Bipolar I disorder	Y	Y
503	15/M/W	Intentional overdose	Y	Y
Double-Blind Taper Phase				
PBO				
5767	12/F/W	Infectious mononucleosis Urinary tract infection	N N	Y Y
2012	14/M/W	Suicidal ideation	N	Y

W=White, Mx=Mixed, M=Male, F=Female, N=No, Y=Yes
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*Reviewer's Comments: During the OL Phase, the most commonly reported SAE was suicidal ideation. Suicidal Behavior and Ideation is listed as a class effect in the Warnings and Precautions Section of Lamictal labeling. In the 5 narratives describing suicidal ideation and behavior which I have summarized above, it is difficult to determine the SAEs were drug-related because an increased risk of suicidal behavior and ideation are known to be associated with bipolar disorder. Two of the subjects (001131 and 001752) were noted to have situational stressors that may have precipitated the suicidality, and two of the subjects (001131 and 002751) had a history of suicidal ideation and/or behavior in the past, presumably when they were not taking Lamictal. On the other hand, one subject (001143) had a reasonable challenge and de-challenge, with suicidal ideation developing (b)(6) days after an increase in Lamictal dose and resolving (b)(6) days after discontinuation. It is unclear whether the fifth case of suicidal ideation (005880), the case of intentional self-injury (001253), or the case of aggression (006240) were related to Lamictal or to the underlying disease (bipolar I disorder). The findings regarding suicidality in Trial **SCA102833** are discussed further in **Section 7.3.4 Significant Adverse Events** below.*

The SAE of impulsive behavior (Subject 002003) may have been due to the patient's noncompliance with lithium. Subject 005772 had a history of asthma and the SAE resolved while the patient was still being treated with lamotrigine, so it is unlikely that Lamictal contributed to the SAE of asthma. Subject 001736 was only on lamotrigine for (b)(6) days when a possible malignant neoplasm was removed from his ankle. Based on what is known about the pathology of tumors, it is improbable that the tumor was caused by lamotrigine in (b)(6) days. The SAE of rash (Subject 001647) was likely due to

LTG because rash is a known adverse event associated with lamotrigine and the rash resolved rapidly after LTG discontinuation.

In the Randomized Phase, only one LTG-treated patient (001637) had an SAE (emotional disorder). The patient had a precipitating stressor (dealing with an alleged sexual assault) and improved despite continuing study medication. Therefore, it is unlikely that this SAE was caused by Lamictal.

7.3.3 Dropouts and/or Discontinuations

Adverse Events Leading to Withdrawal

In the OL Phase, 26 (9%) subjects reported AEs leading to withdrawal, as shown in **Table 59** below. Suicidal ideation (2%), all mania (2%), mania (1%), all rash (1%), agitation (<1%), intentional self-injury (<1%), rash (<1%), and irritability (<1%) were reported in more than 1 subject. All other AEs leading to withdrawal were reported in single subjects.

No subjects reported AEs leading to withdrawal in the OL Taper Phase.

Table 59: Summary of Adverse Events Leading to Withdrawal from Trial with Onset in the OL phase (ITT Population)

Preferred Term	LTG (N=298)
Any event, n (%)	**26 (9)**
Suicidal ideation	7 (2)
All Mania*	5 (2)
-Mania	4 (1)
-Bipolar I disorder	1 (<1)
All Rash*	4 (1)
-Rash	2 (<1)
-Dermatitis allergic	1 (<1)
-Rash generalized	1 (<1)
Agitation	2 (<1)
Intentional self-injury	2 (<1)
Irritability	2 (<1)
Aggression	1 (<1)
Anger	1 (<1)
Anxiety	1 (<1)
Depression	1 (<1)
Pressure of speech	1 (<1)
Restlessness	1 (<1)
Dermatitis	1 (<1)
Neutropenia	1 (<1)
Diarrhoea	1 (<1)
Neoplasm	1 (<1)

*All Mania included the following verbatim terms: bipolar I- worsening (self-harm)- mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, worsening manic symptoms. All Rash included the following verbatim terms: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.
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Narratives for several subjects (Subjects 1143, 1253, 1376, 1647, 1752, 2003, 2751, 5880, and 6240) who developed SAEs which also resulted in withdrawal from the trial are summarized above (**7.3.2 Nonfatal Serious Adverse Events**). Additional narratives of particular interest in patients who received LTG during the OL Phase and developed an AE leading to withdrawal are as follows:

- Subject 1007 (Withdrawal AE: Diarrhea): This 10-year-old male developed diarrhea on 9-1-08, 2 days after start of OL investigational product. The event led to withdrawal from the trial. The AE resolved on 9-10-09. The investigator

considered that there was a reasonable possibility that the event was caused by the investigational product.

- Subject 1137 (Withdrawal AE: Dermatitis allergic): This 15 year-old female with history of eczema received OL investigational product from 8-13-10 to 8-26-10. On 8-24-10, AE of dermatitis allergic (verbatim term: Hypersensitivity and Rash) was reported. The event led to withdrawal from the trial. The AE was recovered/resolved on 9-7-10.
- Subject 1648 (Withdrawal AE: Rash): This 14-year-old male was reported to have an AE of Rash (verbatim term: Skin irritation) on Upper Right Arm) on 7-7-10, 100 days after starting OL investigational product. The event led to early withdrawal from the trial and resolved on 7-15-10.
- Subject 2126 (Withdrawal AE: Neutropenia): This 13-year-old male on lithium carbonate and Seroquel XR received OL investigational product from 11-10-09 until 1-7-10. On 12-24-09, 46 days after the start of investigational product, an AE of Neutropenia (verbatim term: Neutropenia) was reported. The event led to early withdrawal from the trial. The AE was not recovered/not resolved on 1-11-10. The event of neutropenia was considered by the investigator to have a reasonable possibility it was caused by the investigational product.
- Subject 3006 (Withdrawal AE: Intentional self-injury): This 12-year-old female, receiving Depakote and Abilify for bipolar I disorder, was reported to have an AE of Intentional self-injury (verbatim term: Possibly suicidal self-injurious behavior) on 5-9-09, 109 days after the start of OL investigational product. The event led to withdrawal from the trial and was recovered/resolved on 5-9-09, a duration of 1 day. The event was considered by the investigator to have no reasonable possibility it was caused by investigational product.
- Subject 3026 (Withdrawal AE: Dermatitis): This 15 year-old female was receiving Abilify for bipolar I disorder and received OL investigational product from 6-20-12 to 9-4-12. On 8-21-12, an AE of dermatitis (verbatim term: Acute Dermatitis) was reported and led to withdrawal of the subject from the trial. The AE was recovered/resolved with sequelae on 9-30-12 and was considered by the investigator to have reasonable possibility it was caused by the investigational product.
- Subject 4753 (Withdrawal AE: Depression, Suicidal ideation): This 16 year-old male, receiving Abilify and Lithium, received OL investigational product from 5-5-09 until 6-14-09. On 5-24-09, an AE of depression (verbatim term: Worsening Depression) was reported and led to early withdrawal from the trial. The AE was recovered/resolved on 6-8-09. On 5-26-09, an AE of suicidal ideation (verbatim term: Intermittent suicidal Ideation) was reported and led to withdrawal of the subject from the trial. The AE was recovered/resolved on 6-8-09. The subject was withdrawn early from the trial on 6-29-09.
- Subject 4881 (Withdrawal AE: Rash generalized): This 11 year-old female receiving Risperdal for bipolar I disorder and Metadate CD for ADHD received OL investigational product from 6-8-10 until 6-18-10. On 6-17-10, an AE of Rash generalized (verbatim term: All Over Body Rash) was reported and led to

withdrawal from the trial. The AE was recovered/resolved on 7-10-10 and was considered by the investigator to have reasonable possibility it was caused by the investigational product.

- Subject 6236 (Withdrawal AE: Rash): This 17 year-old female received OL investigational product from 10-29-11 until 11-17-11. On 11-14-11, an AE of Rash (verbatim term: Rash on Tops of Both Thighs and Inner Left Forearm) was reported and led to withdrawal from the trial. The AE was recovered/resolved on 11-21-11.

In the Randomized Phase, AEs led to withdrawal in 25 (29%) subjects in the PBO group and 18 (21%) subjects in the LTG group, as shown in **Table 60** below. Of the AEs leading to withdrawal reported in more than 1 subject, the incidence of mania and irritability was higher in the PBO group.

Table 60: Summary of Adverse Events Leading to Withdrawal from Study with Onset in Randomized Phase (Randomized ITT Population)

Preferred Term	PBO (N=86)	LTG (N=87)
Any event, n (%)	**25 (29)**	**18 (21)**
All Mania[b]	7 (8)	5 (6)
-Mania	5 (6)	3 (3)
-Bipolar I disorder	2 (2)	1 (1)
-Bipolar disorder	0	1 (1)
Agitation	1 (1)	3 (3)
Irritability	13 (15)	2 (2)
Aggression	2 (2)	2 (2)
Bipolar I disorder[a]	2 (2)	2 (2)
Anxiety	0	1 (1)
Depression	1 (1)	1 (1)
Retching	0	1 (1)
Vomiting	0	1 (1)
Panic attack	0	1 (1)
Self injurious behavior	0	1 (1)
Suicide attempt	0	1 (1)
Blood thyroid stimulating hormone abnormal	0	1 (1)
Excessive eye blinking	1 (1)	0
Anger	1 (1)	0
Depressed mood	1 (1)	0
Intentional overdose	1 (1)	0
Elevated mood	1 (1)	0
Emotional disorder	1 (1)	0
Insomnia	1 (1)	0
Mood swings	1 (1)	0
Decreased appetite	1 (1)	0
Sedation	1 (1)	0
All Rash[b]	1 (1)	0
-Rash	1 (1)	0

a) One AE of Bipolar I Disorder (preferred term) is not included in the All Mania category because the verbatim term was not one identified or the All Mania category.

b) All Mania included the following verbatim terms: bipolar I- worsening (self-harm)- mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, worsening manic symptoms. All Rash included the following verbatim terms: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.

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In the Double-blind Taper Phase, 1 (2%) subject in the PBO group was withdrawn due to anxiety.

Narratives of particular interest in patients who received LTG during the Randomized Phase and developed an AE leading to withdrawal are as follows:

- Subject 0001 (Withdrawal AE: Suicide Attempt): This 13 year-old male who was receiving ziprasidone for bipolar I disorder and Adderall XR for ADHD received OL investigational product from 12-23-08 and took randomized LTG from 4-21-09 until 1-3-10. On 12-28-09, an AE of Suicide attempt (verbatim term: Suicide Attempt) was reported and led to withdrawal from the trial. The AE was recovered/resolved on 12-28-09, a duration of 1 day.
- Subject 1753 (Withdrawal AE: Blood thyroid stimulating hormone abnormal): This 14 year-old male was receiving lithium for bipolar I disorder and received OL investigational product from 10-9-08 and took randomized LTG from 12-26-08 until 2-8-09. On 12-31-08, an AE of Blood thyroid stimulating hormone (verbatim term: Abnormal Thyroid Stimulating Hormone (TSH) Level) was reported and led to early withdrawal from the trial. The event was considered by the investigator to have no reasonable possibility it was caused by the investigational product.
- Subject 2008 (Withdrawal AE: Vomiting, Retching): This 10 year-old male with ADHD who was receiving Abilify for treatment of bipolar disorder received OL investigational product from 10-10-09 and took randomized LTG from 1-29-10 until 3-11-10. On 2-26-10, AE of vomiting (verbatim term: Emesis) and Retching (verbatim term: Gagging) were reported and led to early withdrawal from the trial. The AE was recovered/resolved on 3-23-10. The events were considered by the investigator to have reasonable probability it was caused by the investigational product.
- Subject 3762 (Withdrawal AE: Panic attack, Self injurious behavior): This 13 year-old female with ADHD who was receiving Abilify for bipolar disorder received OL investigational product from 6-20-12 and took randomized LTG from 9-26-12 until 4-22-13. On 4-9-13, AEs of panic attack (verbatim term: Panic Attacks) and self-injurious behavior (verbatim term: Superficial scratching, Self-injurious behavior) were reported and led to early withdrawal from the trial. The AEs were recovered/resolved on 5-10-13 and were considered by the investigator to have no reasonable probability it was caused by the investigational product.

Reviewer's Comments: In most cases, AEs leading to withdrawal from the trial were known AEs associated with lamotrigine (e.g., rash, dermatitis, vomiting, diarrhea, neutropenia, insomnia) or related to the underlying disease (e.g., all mania, irritability, agitation, panic attack, depressed mood, mood swings, aggression, pressure of speech, restlessness). The possibility of akathisia should be considered in any case of restlessness; however, there was only a single case of restlessness resulting in study withdrawal. Akathisia is discussed in ***Section* 7.3.4 Significant Adverse Events**

below. Suicidal ideation and behavior was discussed above and is discussed further in Section **7.3.4 Significant Adverse Events** *below. The single case of neoplasm was discussed above under SAEs. Subject 1753 was withdrawn from the trial due to blood thyroid stimulating hormone abnormality. This has not been previously reported with Lamictal treatment. Although the investigator concluded that there was no reasonable possibility it was caused by investigational product, it should be reported in labeling.*

Adverse Events Leading to Withdrawal by Age

In the OL Phase, the types and incidence of AEs leading to withdrawal was similar between age subgroups as shown in **Table 61** below. No subjects reported AEs leading to withdrawal in the OL Taper Phase. There are no apparent differences in AEs leading to withdrawal by age, but there are few AEs overall in this category.

Table 61: Summary of Adverse Events leading to Withdrawal by Age with Onset in OL Phase (ITT Population, OL Phase)

Preferred Term	10-12 yrs (N=117)	13-17 yrs (N=181)
Any event, n (%)	**10 (9)**	**16 (9)**
Suicidal ideation	2 (2)	5 (3)
All Mania*	2 (2)	3 (2)
-Mania	2 (2)	2 (1)
-Bipolar I disorder	0	1 (<1)
All Rash*	1 (<1)	3 (2)
-Rash	0	2 (1)
-Dermatitis allergic	0	1 (<1)
-Rash generalized	1 (<1)	0
Agitation	1 (<1)	1 (<1)
Intentional self-injury	1 (<1)	1 (<1)
Irritability	1 (<1)	1 (<1)
Anger	0	1 (<1)
Anxiety	0	1 (<1)
Depression	0	1 (<1)
Dermatitis	0	1 (<1)
Neutropenia	0	1 (<1)
Aggression	1 (<1)	0
Pressure of speech	1 (<1)	0
Restlessness	1 (<1)	0
Diarrhoea	1 (<1)	0
Neoplasm	1 (<1)	0

Note: AEs are ordered by decreasing frequency in the13-17 year old group.
*All Mania included the following verbatim terms: bipolar I- worsening (self-harm)- mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, worsening manic symptoms. All Rash included the following verbatim terms: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin

irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.
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In the Randomized Phase, the incidence of AEs leading to withdrawal was higher in the PBO group for both age groups, as shown in **Table 62** below. The incidence of individual AEs leading to withdrawal was similar between PBO and LTG within each age group with the exception of irritability, which was reported at a higher incidence in the 13-17 year-old subgroup. In the Double-Blind Taper Phase, no AE led to withdrawal in the 10-17 year-old subgroup, and 1 (3%) subject who received PBO was withdrawn in the 13-17 year-old subgroup (anxiety).

Table 62: Summary of Adverse Events Leading to Withdrawal by Age with Onset in Randomized Phase (ITT Population, Randomized Phase)

	10-12 yrs		13-17 yrs	
Preferred Term	PBO N=33	LTG N=33	PBO N=53	LTG N=54
Any event, n (%)	**10 (30)**	**7 (21)**	**15 (28)**	**11 (20)**
All Mania[a]	3 (9)	3 (9)	4 (8)	2 (4)
-Mania	3 (9)	2 (6)	2 (4)	1 (2)
-Bipolar I disorder	0	1 (3)	2 (4)	1 (2)
Agitation	1 (3)	0	0	3 (6)
Irritability	2 (6)	0	11 (21)	2 (4)
Bipolar I disorder[a]	0	1 (3)	2 (4)	1 (2)
Mania	3 (9)	2 (6)	2 (4)	1 (2)
Aggression	1 (3)	1 (3)	1 (2)	1 (2)
Anxiety	0	0	0	1 (2)
Panic attack	0	0	0	1 (2)
Self injurious behavior	0	0	0	1 (2)
Suicide attempt	0	0	0	1 (2)
Blood thyroid stimulating hormone abnormal	0	0	0	1 (2)
Anger	0	0	1 (2)	0
Depressed mood	0	0	1 (2)	0
Depression	0	1 (3)	1 (2)	0
Elevated mood	0	0	1 (2)	0
Insomnia	0	0	1 (2)	0
Mood swings	0	0	1 (2)	0
Intentional overdose	0	0	1 (2)	0
Bipolar disorder	0	1 (3)	0	0
Emotional disorder	1 (3)	0	0	0
Excessive eye blinking	1 (3)	0	0	0
Retching	0	1 (3)	0	0
Vomiting	0	1 (3)	0	0
Decreased appetite	1 (3)	0	0	0
Sedation	1 (3)	0	0	0
All Rash	1 (3)	0	0	0
-Rash	1 (3)	0	0	0

a) One AE of Bipolar I Disorder (preferred term) is not included in the All Mania category because the verbatim term was not one identified or the All Mania category

Note: AEs are ordered by decreasing frequency in the13-17 year old group.

*All Mania included the following verbatim terms: bipolar I- worsening (self-harm)- mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, worsening manic symptoms. All Rash included the following verbatim terms: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.

Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 54, page 119.

7.3.4 Significant Adverse Events

Suicidal Ideation and Behavior

Columbia Suicide Severity Rating Scale:

Suicidal ideation and behavior was monitored at each visit during the trial using the Columbia Suicide Severity Rating Scale (C-SSRS). Of the subjects in the OL Phase, a total of 52 (17%) had an event recorded on the C-SSRS (any event, 1-10). A total of 52 (17%) had an event recorded for suicidal ideation (any suicidal ideation, 1-5), as shown in **Table 63** below. A total of 4 (1%) subjects had an event recorded for suicidal behavior (any suicidal behavior, 6-10) including a subject with a Possible Suicide-Related Adverse Event (PSRAE) of failed suicide attempt (Subject 1765).

In the OL Phase, C-SSRS ratings by age were similar to the Overall population (**Table 63**).

In the OL Taper Phase, 3 (9%) subjects had an event recorded for suicidal ideation (any suicidal ideation, 1-5). None had events recorded for suicidal behavior (**Table 63**). In the OL Taper Phase, C-SSRS ratings by age were similar to the Overall population.

Table 63: Summary of Number of Subjects [n(%)] in C-SSRS Suicide Categories during OL Phase and OL Taper Phase by Age Subgroup and Overall Population

Treatment Phase	OL			OL Taper		
Group or Sub-group	**Age 10-12 years (N=117)**	**Age 13-17 years (N=181)**	**Overall (N=298)**	**Age 10-12 years (N=16)**	**Age 13-17 years (N=19)**	**Overall (N=35)**
Number of subjects with at least one C-SSRS assessment completed post-baseline	***116 (>99)***	***181 (100)***	***297 (>99)***	***16 (100)***	***19 (100)***	***35 (100)***
Suicide Ideation or Behavior (1-10)~ Any event	21 (18)	31 (17)	52 (17)	2 (13)	1 (5)	3 (9)
Suicidal Ideation (1-5)~ Any suicidal ideation	***21 (18)***	***31 (17)***	***52 (17)***	***2 (13)***	***1 (5)***	***3 (9)***
1 – Wish to be dead	14 (12)	22 (12)	36 (12)	2 (13)	1 (5)	3 (9)
2 – Non-specific active suicidal thoughts	7 (6)	8 (4)	15 (5)	0	0	0
3 – Active suicidal ideation with any methods (not plan) without intent to act	4 (3)	11 (6)	15 (5)	0	0	0
4 – Active suicidal ideation with some intent to act, without specific plan	0	1 (<1)	1 (<1)	0	0	0
5 – Active suicidal ideation with specific plan and intent	0	2 (1)	2 (<1)	0	0	0
Suicidal behavior (6-10) ~ Any suicidal behavior	***2 (2)***	***2 (1)***	***4 (1)***	***0***	***0***	***0***
6 - Preparatory acts or behavior	0	1 (<1)	1 (<1)	0	0	0
7 – Aborted attempt	1 (<1)	1 (<1)	2 (<1)	0	0	0
8 – Interrupted attempt	0	1 (<1)	1 (<1)	0	0	0
9 – Non-fatal actual suicide attempt	1 (<1)	1 (<1)	2 (<1)	0	0	0
10 – Completed suicide	0	0	0	0	0	0

Source: Clinical Study Report; SCA 102833, Tables 55 (page 120), 26.7 (pages 1821-1822), 26.3 (page 1817), and 26.9 (pages 1825-1826)

Of the subjects in the Randomized Phase, a total of 10 (11%) subjects in the LTG group had an event recorded on the C-SSRS (any event, 1-10) compared to 6 (7%) in the PBO group, as shown in **Table 64** below. Ten (11%) subjects in the LTG group had an event recorded for suicidal ideation (any suicidal ideation, 1-5) compared with 6 (7%) in the PBO group. One (1%) subject in the LTG group had an event recorded for suicidal behavior (any suicidal behavior, 6-10) which was also considered a PSRAE (preferred term of "suicide attempt," Subject 0001).

In the Randomized Phase, C-SSRS ratings by age were similar to the Overall population (**Table 65**).

In the Double-blind Taper Phase, 2 (3%) subjects in both the LTG and PBO groups had an event recorded on the C-SSRS (any event, 1-10) (**Table 64**). The number of subjects with suicidal ideation or behavior events on the C-SSRS was small and was similar between the two treatment groups (**Table 65**). In the Double-blind Taper Phase, C-SSRS ratings by age were similar to the Overall population.

Table 64: Summary of Number of Subjects in the C-SSRS Suicide Categories during the Randomized Phase (Randomized ITT Population)

	Randomized Phase		Double Blind Taper Phase	
	PBO (N=86)	LTG (N=87)	PBO (N=55)	LTG (N=52)
Number of subjects with at least one C-SSRS assessment completed post-baseline	85	87	55	52
Suicidal Ideation or Behavior (1-10)~ Any event	6 (7)	10 (11)	2 (4)	2 (4)
Suicidal Ideation (1-5)~ Any suicidal ideation	6 (7)	10 (11)	2 (4)	1 (2)
1 - Wish to be dead	5 (6)	6 (7)	1 (2)	1 (2)
2 - Non-specific active suicidal thoughts	1 (1)	0	0	0
3 - Active suicidal ideation with any methods (not plan) without intent to act	1 (1)	3 (3)	0	0
4 - Active suicidal ideation with some intent to act, without specific plan	0	0	1 (2)	0
5 - Active suicidal ideation with specific plan and intent	0	1 (1)	1 (2)	0
Suicidal behavior (6-10) ~ Any suicidal behavior	0	1 (1)	1 (2)	1 (2)
6 - Preparatory acts or behavior	0	1 (1)	0	1 (2)
7 - Aborted attempt	0	0	1 (2)	0
8 - Interrupted attempt	0	1 (1)	0	0
9 - Non-fatal actual suicide attempt	0	1 (1)	0	0
10 - Completed suicide	0	0	0	0

Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 56, page 121.

Table 65: Summary of Number of Subjects [n(%)] in C-SSRS Suicide Categories during Randomized Phase and Double-blind Taper Phase by Age Subgroup

Treatment Phase	Randomized (N=173)				Double-blind Taper			
Group or Sub-group	Age 10-12 years (N=66)		Age 13-17 years (N=106)		Age 10-12 years (N=107)		Age 13-17 years (N=108)	
Treatment	PBO (N=33)	LTG (N=33)	PBO (N=52)	LTG (N=54)	PBO (N=55)	LTG (N=53)	PBO (N=55)	LTG (N=53)
Number of subjects with at least one C-SSRS assessment completed post-baseline	***33 (100)***	***33 (100)***	***52 (100)***	***54 (100)***	***22 (40)***	***21 (40)***	***33 (60)***	***31 (60)***
Suicide Ideation or Behavior (1-10)~ Any event	2 (6)	4 (12)	4 (8)	6 (11)	0	2 (10)	2 (6)	0
Suicidal Ideation (1-5)~ Any suicidal ideation	***2 (6)***	***4 (12)***	***4 (8)***	***6 (11)***	***0***	***1 (5)***	***2 (6)***	***0***
1 – Wish to be dead	2 (6)	3 (9)	3 (6)	3 (6)	0	1 (5)	1 (3)	0
2 – Non-specific active suicidal thoughts	0	0	1 (2)	0	0	0	0	0
3 – Active suicidal ideation with any methods (not plan) without intent to act	1 (3)	1 (3)	0	2 (4)	0	0	0	0
4 – Active suicidal ideation with some intent to act, without specific plan	0	0	0	0	0	0	1 (3)	0
5 – Active suicidal ideation with specific plan and intent	0	0	0	1 (2)	0	0	1 (3)	0
Suicidal behavior (6-10) ~ Any suicidal behavior	***0***	***0***	***0***	1 (2)	***0***	***1 (5)***	1 (3)	***0***
6 - Preparatory acts or behavior	0	0	0	1 (2)	0	1 (5)	0	0
7 – Aborted attempt	0	0	0	0	0	0	1 (3)	0
8 – Interrupted attempt	0	0	0	1 (2)	0	0	0	0
9 – Non-fatal actual suicide attempt	0	0	0	1 (2)	0	0	0	0
10 – Completed suicide	0	0	0	0	0	0	0	0

Source: Clinical Study Report; SCA 102833, Tables 56 (page 121), 26.8 (pages 1823-1824), and 26.10 (pages 1827-1828)

New or Worsening Suicidal Behavior:

Ten (11%) subjects in the LTG group and 6 (7%) subjects in the PBO group had a rating of new or worsened suicidal ideation or behavior during the Randomized Phase, as shown in **Table 66** below.

Table 66: Summary of New or Worsened Suicidal Ideation or Behavior during the Randomized Phase

Number (%) of Subjects with New or Worsened Suicidal Ideation or Behavior	PBO (N=86)	LTG (N=87)	Total (N=173)
Suicidal ideation (1-5)[a]	6/85 (7)	10/87 (11)	16/172 (9)
More severe suicidal ideation (4-5)[a]	0/85	1/87 (1)	1/172 (<1)
Suicidal behavior (6-10)	0/85	1/87 (1)	1/172 (<1)
Suicidal ideation or behavior (1-10)	6/85 (7)	10/87 (11)	16/172 (9)

a. The denominator is the number of subjects with Randomization Visit C-SSRS score <5.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 57, page 121.

There did not appear to be differences between treatment groups. The data by age were similar to the Overall population, as shown in **Table 67** below.

Table 67: Summary of New or Worsened Suicidal Ideation or Behavior during Randomized Phase by Age Group (Number (%) of Subjects)

Age Group	Ideation of Behavior	PBO (N=86)	LTG (N=87)	Total (N=173)
10-12	Suicidal ideation (1-5)	2/33 (6%)	4/33 (12%)	6/66 (9%)
	More severe suicidal ideation (4-5)	0/33	0/33	0/66
	Suicidal behavior (6-10)	0/33	0/33	0/66
	Suicidal ideation or behavior (1-10)	2/33 (6%)	4/33 (12%)	6/66 (9%)
13-17	Suicidal ideation (1-5)	4/52 (8%)	6/54 (11%)	10/106 (9%)
	More severe suicidal ideation (4-5)	0/52	1/54 (2%)	1/106 (<1%)
	Suicidal behavior (6-10)	0/52	1/54 (2%)	1/106 (<1%)
	Suicidal ideation or behavior (1-10)	4/52 (8%)	6/54 (11%)	10/106 (9%)

The denominator is the number of subjects with Randomization Visit C-SSRS score <5.
Note: Subject excluded if no post baseline assessment was available.
Source: Clinical Study Report; SCA 102833, Table 26.11, page 1829.

A maximum of two subjects in either treatment group had a rating of new or worsened suicidal ideation or behavior during the Double-blind Taper phase relative to the Randomized Visit, as shown in **Table 68** below. There did not appear to be differences between treatment groups. The data by age were similar to the Overall population (**Table 69**).

Table 68: Summary of New or Worsened Suicidal Ideation or Behavior during Double-blind Taper Phase

Number (%) of Subjects with New or Worsened Suicidal Ideation or Behavior	PBO (N=55)	LTG (N=53)	Total (N=108)
Suicidal ideation (1-5) [a]	2/55 (4)	1/52 (2)	3/107 (3)
More severe suicidal ideation (4-5) [a]	2/55 (4)	0	2/107 (2)
Suicidal behavior (6-10)	1/55 (2)	1/52 (2)	2/107 (2)
Suicidal ideation or behavior (1-10)	2/55 (4)	2/52 (4)	4/107 (4)

a. The denominator is the number of subjects with Randomization Visit C-SSRS score <5.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 58, page 122.

Table 69: Summary of New or Worsened Suicidal Ideation or Behavior during Double-blind Taper Phase by Age Group (Number (%) of Subjects)

Age Group	Ideation of Behavior	PBO (N=55)	LTG (N=53)	Total (N=108)
10-12	Suicidal ideation (1-5)	0/22	1/21 (5%)	1/43 (2%)
	More severe suicidal ideation (4-5)	0/22	0/21	0/43
	Suicidal behavior (6-10)	0/22	1/21 (5%)	1/43 (2%)
	Suicidal ideation or behavior (1-10)	0/22	2/21 (10%)	2/43 (5%)
13-17	Suicidal ideation (1-5)	2/33 (6%)	0/31	2/64 (3%)
	More severe suicidal ideation (4-5)	2/33 (6%)	0/31	2/64 (3%)
	Suicidal behavior (6-10)	1/33 (3%)	0/31	1/64 (2%)
	Suicidal ideation or behavior (1-10)	2/33 (6%)	0/31	2/64 (3%)

The denominator is the number of subjects with Randomization Visit C-SSRS score <5.
Note: Subject excluded if no post baseline assessment was available.
Source: Clinical Study Report; SCA 102833, Table 26.12, page 1830.

Possible Suicidality-Related Adverse Events (PSRAEs):

Overall, in the entire trial, a total of 28 (7%) subjects reported a total of 36 Possible Suicide-Related Adverse events (PSRAEs). There were no completed suicides. In the OL Phase and OL Taper Phase, 21 subjects reported a total of 25 PSRAEs (of the 21 subjects, 1 had an event in the OL and OL Taper Phases and 2 also had an event in the Randomized Phase), as shown in **Table 70** below. In the OL Phase, 20 subjects reported 23 PSRAEs. Subject 1765 reported a failed suicide attempt that was not considered an SAE and did not lead to discontinuation. Five subjects were withdrawn from the trial due to PSRAE, and 7 subjects reported PSRAEs as SAEs. In the OL Taper Phase, 2 subjects reported PSRAEs (one also had an event in the OL Phase). Neither of these events was SAEs or led to discontinuation from the trial.

Table 70: Summary of PSRAEs with Onset in the OL Phase or OL Taper Phase – An Overview (OL and OL Taper ITT Population)

	OL (N=298)	OL Taper (N=35)
All PSRAEs, n (%)	**20 (7)**	**2 (6)**
AEs leading to study discontinuation	5 (2)	0
AEs related to study treatment	0	0
AEs leading to dose reduction	0	0
AEs leading to dose interruption/delay	0	0
All PSRAE SAE, n (%)	7 (1)	**0**
SAEs related to study treatment	1 (<1)	0
Fatal SAEs	0	0

Note: Subjects can be included in more than one category.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 59, page 122.

In the Randomized Phase and Double-Blind Taper Phase, 9 subjects reported a total of 11 PSRAEs (of the 9 subjects, 1 had an event in the Randomized and Double-blind Phases), as shown in **Table 71** below. In the Randomized Phase, PSRAEs were reported by a total of 1 (1%) subject in the PBO group and 6 (7%) subjects in the LTG group. One subject in the LTG group (Subject 0001) reported a failed suicide attempt. The event led to discontinuation from the trial but was not considered an SAE.

In the Double-Blind Taper Phase, PSRAEs were reported by a total of 2 (3%) subjects in the PBO group (one of these subjects reported 2 events in the Double-Blind Taper Phase) and 1 (2%) subject in the LTG group (this subject also reported a PSRAE in the Randomized Phase) (**Table 71**). None of the events were considered SAEs, but one subject in the PBO group was discontinued from the trial due to the PSRAE.

Table 71: Summary of PSRAEs with Onset in the Randomized Phase or Double-Blind Taper Phase – An Overview (Randomized and Double-Blind Taper ITT Population)

	Randomized		Double-blind Taper	
	PBO (N=86)	LTG (N=87)	PBO (N=55)	LTG (N=53)
Any PSRAE, n (%)	1 (1)	6 (7)	**2 (3)**	**1 (2)**
AEs leading to study discontinuation	1 (1)	1 (1)	1 (2)	0
AEs related to study treatment	0	0	0	0
AEs leading to dose reduction	0	0	0	0
AEs leading to dose interruption/delay	0	0	0	0
Any PSRAE, n (%)	0	0	**0**	**0**
SAEs related to study treatment	0	0	0	0
Fatal SAEs	0	0	0	0

Note: Subjects can be included in more than one category.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 60, page 123.

Of the 28 subjects reporting PSRAEs, 10 (9%) were in the 10-12 year-old age subgroup and 18 (10%) were in the 13-17 year-old age subgroup. In the 10-12 year-old age subgroup, 3 events were considered an SAE and 7 led to withdrawal. In the 13-17 year-old age subgroup, 5 events were considered SAEs, and 7 led to withdrawal. The tables below (**Table 72**, **Table 73**, and **Table 74**) provide line listings of subjects reporting PSRAEs by age subgroup and treatment (LTG versus PBO). Note that no subjects in the 10-12 year-old subgroup were reported to have PSRAEs while receiving PBO. Therefore, there is no table of line listings for this subgroup.

Table 72: Line Listing of Subjects (10-12 Year-Old Subgroup) Reporting PSRAEs While Receiving LTG

Subject	Age/ Sex/ Race	Phase	Event	Withdrawn Y/N	SAE Y/N	Days after 1st dose (days after last dose change)	C-SSRS (Items 1-5) Y/N		C-SSRS (Items 6-10) Y/N	
							Baseline	Visit Prior	Baseline	Visit Prior
4128	10/F/W	Rand	Suicidal ideation	N	N	145 (1)	N	N	N	N
		OL	Suicidal ideation	N	N	62 (50)	N	N	N	N
3763	10/F/W	Rand	Parent reported subject threatened to shoot self after being disciplined. Subject denies saying	N	N	198 (155)	N	N	N	N
1768	11/F/W	Rand	Wish to be dead	N	N	133 (91)	N	N	N	N
		DB taper	Wish to be dead	N	N	171 (12)	N	N	N	N
1127	11/F/W	OL	Fleeting suicidal thoughts 3 times	N	N	9 (9)	N	N	Y	Y
		OL	One episode of passive suicidal thoughts	N	N	29 (1)	N	N	Y	N
2879	12/M/B	OL	Suicidal ideation	N	Y	100 (43)	N	N	N	N
3006	12/F/W	OL	Possibly suicidal self injurious behavior	N	Y	108 (2)	N	N	N	N
1765	11/M/W	OL	Failed suicide attempt	N	N	(b) (6)	Y		N	
		OL	Suicidal ideation	N	N	24 (10)	Y	N	N	N
1766	11/M/W	OL taper	Wish to be dead	N	N	69 (6)	N	N	N	N
		OL	Wish to be dead	N	N	48 (6)	N	N	N	N
1793	10/M/W	OL	Suicidal ideations	N	N	14 (16)	Y	N	N	N
5880	12/F/Mx	OL	Written suicidal ideation	Y	Y	(b) (6)	Y	Y	N	N

W=White, B=Black, Mx=Mixed, M=Male, F=Female, N=No, Y=Yes
Source: Clinical Study Report; SCA 102833, Table 61, pages 124-125.

Table 73: Line Listing of Subjects (13-17 Year-Old Subgroup) Reporting PSRAEs While Receiving LTG

Subject	Age /Sex/ Race	Phase	Event	Withdrawn Y/N	SAE Y/N	Days after 1st dose (days after last dose change)	C-SSRS (Items 1-5) Y/N		C-SSRS (Items 6-10) Y/N	
							Baseline	Visit Prior	Baseline	Visit Prior
1879	14/F/W	OL	Suicidal ideation	N	N	3 (3)	N	N	N	N
1001	13/M/W	Rand	Transient wish to be dead	N	N	125 (60)	Y	N	N	N
5377	15/F/W	Rand	Suicidal ideation	N	N	167 (96)	Y	N	Y	N
		OL	Suicidal ideation without intent	N	N	25 (10)	Y	N	Y	N
5379	13/W/M	OL	Active suicidal ideation without intent	N	N	1 (1)	Y	Y	Y	Y
0001	13/M/W	Rand	Suicide attempt	Y	N	(b) (6)	N	N	N	N
504	13/M/W	OL	Intermittent suicidal ideation	N	N	1 (1)	N	N	N	N
1776	16/M/W	OL	Wish to be dead	N	N	21 (7)	N	N	N	N
1131	17/F/W	OL	Presenting with suicidal thoughts	Y	Y	58 (2)	Y	Y	Y	Y
1143	13/F/W	OL	Hospitalization for suicidal ideation	Y	Y	(b) (6)	Y	N	N	N
4753	16/M/W	OL	Intermittent suicidal ideations	N	N	22 (8)	Y	N	N	N
2751	16/F/W	OL	Suicidal ideation	Y	Y	(b) (6)	Y	N	Y	N
1751	13/F/W	OL taper	Wish to be dead	N	N	37 (9)	N	N	N	N
1752	16/F/W	OL	Worsening of suicidal ideation	N	N	8 (8)	Y	Y	Y	Y
		OL	Worsening of suicidal ideation	Y	Y	(b) (6)	Y	Y	Y	Y
1257	13/F/W	OL	Superficial suicidal attempt and thoughts	N	N	61 (12)	N	N	N	N
390	17/F/B	OL	Suicidal ideation	N	N	22 (6)	Y	N	N	N

W=White, B=Black, Mx=Mixed, M=Male, F=Female, N=No, Y=Yes
Source: Clinical Study Report; SCA 102833, Table 61, pages 124-125.

Table 74: Line Listing of Subjects (13-17 Year-Old Subgroup) Reporting PSRAEs While Receiving PBO*

Subject	Age /Sex/ Race	Phase	Event	Withdrawn Y/N	SAE Y/N	Days after 1st dose (days after last dose change)	C-SSRS (Items 1-5) Y/N		C-SSRS (Items 6-10) Y/N	
							Baseline	Visit Prior	Baseline	Visit Prior
2012	14/M/W	DB taper	Suicidal threat	Y	N	285 (4)	N	N	N	N
503	15/M/W	Rand	Intentional drug overdose	Y	Y	(b) (6)	N	N	N	N
1757	14/M/W	DB taper	Suicidal ideation	N	N	149 (7)	Y	N	N	N
		DB taper	Suicidal ideation	N	N	146 (4)	Y	Y	N	N

W=White, B=Black, Mx=Mixed, M=Male, F=Female, N=No, Y=Yes
*Note: No subjects in the 10-12 year-old subgroup were reported to have PSRAEs while taking PBO.
Source: Clinical Study Report; SCA 102833, Table 61, pages 124-125.

The sponsor has concluded that there was no apparent pattern with respect to gender, age, when events occurred (days after 1st dose or days since last dose change), nor was there a pattern with respect to Baseline C-SSRS score or the C-SSRS score at the visit prior to the event. The sponsor notes that a number of subjects reported PSRAEs within 2 weeks of a dose increase, but the sponsor reasons that this may have been largely secondary to the dosing titration schedule during the OL phase of the trial.

*Reviewer's Comments: The data provided from Trial **SCA102833** indicate an increased risk of suicide ideation and behavior in children and adolescents receiving Lamictal compared to children and adolescents taking placebo. However, the risk of suicidal ideation and behavior in patients treated with Lamictal is already included in the Warnings and Precautions section of Lamictal labeling (**Section 5.4**). The labeling specifically states, "AEDs, including Lamictal, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication." I have discussed the findings from Trial **SCA102833** with Dr. Marc Stone, Senior Medical Reviewer on the DPP safety Team. Dr. Stone calculated the following odds ratios from the data provided:*

1. *Number of Subjects in C-SSRS Suicide Categories during Randomized Phase (PBO vs. LTG;* **Table 64***): odds ratio 1.7 (0.5 to 6.0, **p=0.43**)*
2. *Number of Subjects in C-SSRS Suicide Categories during Randomized Phase by Age Group (PBO vs. LTG;* **Table 65***): Age10-12: odds ratio 2.1 (0.3 to 25, p=**0.67**); Age 13-17: odds ratio 1.0 (0.2 to 5.5, p=**1.00**)*
3. *Number of Subjects with New or Worsened Suicidal Ideation or Behavior during Randomized Phase (PBO vs. LTG;* **Table 66***): odds ratio 1.7 (0.5 to 6.0, **p=0.43**)*
4. *Number of Subjects with New or Worsened Suicidal Ideation or Behavior during Randomized Phase (PBO vs. LTG;* **Table 67***) by age group: Age10-12: odds ratio 2.1 (0.3 to 25, **p=0.67**); Age 13-17: odds ratio 1.5 (0.3 to 7.7, **p=0.74**)*
5. *Summary of PSRAEs with onset in Randomized Phase (any PSRAE;* **Table 71***): odds ratio 6.3 (0.7 to 292, **p=0.11**).*

*Thus, none of the odds ratios calculated above reach statistical significance. In email correspondence to this reviewer on 8 December 2014, Dr. Stone writes that the suicidality findings from Trial **SCA102833** are not statistically impressive and are "consistent with what we've seen in other trials." Thus, I recommend no changes to Lamictal labeling regarding the risk of suicide ideation and behavior based on the results of Trial **SCA102833**.*

Rash

The sponsor conducted a search of preferred and verbatim terms. Preferred and verbatim terms that were clearly not drug related as judged by medical review were excluded from the "all rash" category. For this reason, the incidence of dermatological AEs differs from that in "All Rash." The remaining verbatim terms comprise the "All Rash" preferred term. The verbatim terms identified that comprise the "All Rash" category were: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.

"All Rash" events in the OL and OL Taper Phases are summarized in **Table 75** below. A total of 11 (4%) subjects reported 13 "All Rash" events in the OL Phase. Five of the events led to withdrawal of 4 subjects. One (0.3%) of these events was considered an SAE:

- Subject 1647 who was receiving 25 mg of LTG and was also receiving concomitant valproate (VPA), developed a rash (b) (6) days after the start of LTG. The subject was hospitalized and withdrawn from the trial. In the opinion of the investigator, the rash may have been drug-related. The event resolved after one day.

Table 75: Summary of "All Rash" Adverse Events with Onset in the OL Phase or OL Taper Phase – An Overview (OL and OL Taper ITT Population)

	OL (N=298)	OL Taper (N=35)
All Rash, n (%)	11 (4)	**0**
AEs leading to permanent discontinuation of study treatment	5 (2)	0
AEs leading to study discontinuation	4 (1)	0
AEs related to study treatment	5 (2)	0
AEs leading to dose reduction	0	0
AEs leading to dose interruption/delay	1 (<1)	0
Dermatological/Hypersensitivity AE	11 (4)	**0**
All Rash SAE, n (%)	1 (<1)	**0**
SAEs related to study treatment	1 (<1)	0
Fatal SAEs	0	0

Note: Subjects can be included in more than one category.
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"All Rash" events in the Randomized and Double-Blind Taper Phases are summarized in **Table 76** below. In the Randomized Phase, 2 (2%) subjects in the LTG group reported 3 "All Rash" events and 1 (1%) subject in the PBO group reported 1 "All Rash:" event. Of these events, none was an SAE and 1 event was an AE leading to withdrawal.

Table 76: Summary of "All Rash" Adverse Events with Onset in the Randomized Phase or Double-Blind Taper Phase – An Overview (Randomized and Double-Blind Taper ITT Population)

	Randomized		Double-blind Taper	
	PBO (N=86)	LTG (N=87)	PBO (N=55)	LTG (N=53)
Any AE, n (%)	1 (1)	2 (2)	**0**	**0)**
AEs leading to permanent~ discontinuation of study treatment	1 (1)	0	0	0
AEs leading to study discontinuation	1 (1)	0	0	0
AEs related to study treatment	0	0	0	0
AEs leading to dose reduction	0	0	0	0
AEs leading to dose interruption/delay	0	0	0	0
Dermatological/Hypersensitivity AE	1 (1)	2 (2)	**0**	**0**
Any SAE, n (%)	0	0	**0**	**0**
SAEs related to study treatment	0	0	0	0
Fatal SAEs	0	0	0	0

Note: Subjects can be included in more than one category.
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Line listing for all subjects reporting "All Rash" events are shown in **Table 77** below. All of the events resolved with the exception of one event that was considered resolving.

There were no events of Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN).

Table 77: Subjects Reporting "All Rash" Events (ITT Population, OL, and OL Taper, Randomized and Double-Blind Taper Phases)

Subject/Bipolar Med Group	Age/Sex/Race	Preferred Term/Verbatim term	Days since first dose	SAE Y/N	Withdrawn Y/N	Resolved Y/N	Severity
Open-Label Phase							
1151/CBZ	17/M/W	Rash/Rash	86 LTG	N	N	Y	Mild
1647/VPA	14/M/W	Rash/Rash	(b) (6) LTG	Y	Y	Y	Severe
		Rash/Rash		N	Y	Y	Severe
1648/VPA	14/M/W	Rash/Rash (skin irritation) on upper right arm	99 LTG	N	Y	Y	Moderate
1137/Neutral	15/F/W	Dermatitis allergic/hypersensitivity and rash	12 LTG	N	Y	Y	Severe
1651/Neutral	15/F/Mx	Purpura/Skin rash (purpura)	94 LTG	N	N	Y	Moderate
4881/Neutral	11/F/W	Rash generalized/all over body rash	10 LTG	N	Y	Y	Severe
3629/Neutral	11/M/W	Dermatitis/Rash- upper abdomen- dermatitis	32 LTG	N	N	Y	Mild
1141/Neutral	16/M/W	Rash papular/Papular rash	40 LTG	N	N	Y	Mild
398/Neutral	17/F/W	Rash/Rash	21 LTG	N	N	Y	Mild
		Rash/Rash	14 LTG	N	N	Y	Mild
6236/Neutral	17/F/W	Rash/Rash on tops of both thighs and inner left forearm	17 LTG	N	N	Y	Mild
1133/Neutral	11/F/W	Rash/Rash	48 LTG	N	N	Y	Mild
OL Taper Phase							
none	NA	NA		NA	NA	NA	NA
LTG Randomized Phase							
399/Neutral	10/F/W	Rash/Rash	80 LTG	N	N	Y	Moderate
1879/Neutral	14/F/W	Rash/Rash on chest and armpits	168 LTG	N	N	Y	Mild
		Rash/Rash on chest and legs	167 LTG	N	N	Y	Mild
PBO Randomized Phase							
402/Neutral	11/M/W	Rash/Rash	83 LTG / 13 PBO	N	Y	Y	Mild

W=White, B=Black, M=Male, F=Female, N=No, Y=Yes, NA=Not Applicable
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 64, page 128.

*Reviewer's Comments: In Trial **SCA102833**, no subject experienced Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). Current Lamictal Labeling includes risk of serious skin rashes under **Warnings and Precautions** (**Section 5.1**). The risk of rash in subjects treated with Lamictal is well-known. The findings from Trial **SCA102833** are consistent with current Lamictal labeling.*

Abnormal Involuntary Movement Scales

AIMS Score:

In the OL Phase, the mean change from Screening to OL week 18 or early withdrawal for AIMS total score was 0.1 (SD 0.73). The mean change for all of the individual items and Total Score (Sum of items 1-7) was negligible (**Table 78**).

Table 78: Summary of Abnormal Involuntary Movement (AIMS) Severity Scores – Open Label Phase (OL ITT Population)

		LTG (N=298)
AIMS Total Score (Sum of Items 1-7)		
Screening visit	n	279
	Mean (SD)	0.13 (0.684)
OL week 18 / early w/d	n	279
	Mean (SD)	0.13 (0.735)
Change from Screening visit to OL WK 18 / EARLY W/D	n	279
	Mean (SD)	0.00 (0.886)
AIMS Overall Severity Index Score (Item 8)		
Screening visit	n	279
	Mean (SD)	0.03 (0.206)
OL week 18 / early w/d	n	279
	Mean (SD)	0.04 (0.265)
Change from Screening visit to OL WK 18 / EARLY W/D	n	279
	Mean (SD)	0.01 (0.317)
AIMS Incapacitation Score (Items 9)		
Screening visit	n	279
	Mean (SD)	0.01 (0.146)
OL week 18 / early w/d	n	279
	Mean (SD)	0.01 (0.120)
Change from Screening visit to OL WK 18 / EARLY W/D	n	279
	Mean (SD)	-0.01 (0.190)
AIMS Awareness Score (Item 10)		
Screening visit	n	279
	Mean (SD)	0.05 (0.257)
OL week 18 / early w/d	n	279
	Mean (SD)	0.04 (0.237)
Change from Screening visit to OL WK 18 / EARLY W/D	n	279
	Mean (SD)	-0.01 (0.344)

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For the Randomized Phase, the mean change from Randomization to Week 36/early withdraw for the AIMS total score (Sum items 1-7) and individual items was negligible (**Table 79**). The mean differences (LTG-PBO) indicated no difference between the groups.

Table 79: Summary of Abnormal Involuntary Movement (AIMS) Severity Scores – Randomization Phase (Randomized ITT Population)

		PBO (N=86)	LTG (N=87)	LTG-PBO Mean DIFF (Lower CI, Upper CI)
AIMS Total Score (Sum of Items 1-7)				
Randomization visit	n	83	83	
	Mean (SD)	0.06 (0.36)	0.18 (0.70)	
Ran week 36 / early w/d	n	83	83	
	Mean (SD)	0.05 (0.27)	0.07 (0.34)	
Change from Randomization to RAN WK 36 / EARLY W/D	n	83	83	
	Mean (SD)	-0.01 (0.43)	-0.11 (0.72)	
				-0.096 (-0.277, 0.084)
AIMS Overall Severity Index Score (Item 8)				
Randomization visit	n	83	83	
	Mean (SD)	0.00 (0.00)	0.07 (0.30)	
Ran week 36 / early w/d	n	83	83	
	Mean (SD)	0.01 (0.11)	0.01 (0.11)	
Change from Randomization to RAN WK 36 / EARLY W/D	n	83	83	
	Mean (SD)	0.01 (0.11)	-0.06 (0.29)	
				-0.072 (-0.139,-0.006)
AIMS Incapacitation Score (Items 9)				
Randomization visit	n	83	83	
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	
Ran week 36 / early w/d	n	83	83	
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	
Change from Randomization to RAN WK 36 / EARLY W/D	n	83	83	
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	
				0.000 (N/C , N/C)
AIMS Awareness Score (Item 10)				
Randomization visit	n	83	83	
	Mean (SD)	0.01 (0.11)	0.05 (0.22)	
Ran week 36 / early w/d	n	83	83	
	Mean (SD)	0.04 (0.19)	0.01 (0.11)	
Change from Randomization to RAN WK 36 / EARLY W/D	n	83	83	
	Mean (SD)	0.02 (0.22)	-0.04 (0.24)	
				-0.060 (-0.131, 0.011)

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Simpson Angus Score (SAS):

The change from randomization to Week 36/early withdrawal was 0.1 (-0.13, 0.29) indicating no difference between treatment groups (**Table 80**).

Table 80: Summary of Simpson Angus Total Score (OL and Randomized ITT Populations)

	PBO			LTG			LTG-PBO		
	n	Mean	SD	n	Mean	SD	Mean DIFF	Lower CI	Upper CI
Baseline				217	0.19	0.65			
OL week 18 / early w/d				223	0.16	0.52			
Change from BASELINE to OL WK 18 / EARLY W/D				200	-0.01	0.70			
Randomization	67	0.19	0.58	69	0.14	0.52			
Ran week 36 / early w/d	74	0.07	0.25	71	0.11	0.43			
Change from Randomization to RAN WK 36 / EARLY W/D	62	-0.11	0.55	62	-0.03	0.65	0.08	-0.13	0.30

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Barnes Akathisia Global Assessment:

There was no statistically significant change from Randomization to Week 36/Early Withdrawal. There was no statistically significant difference between LTG and PBO on any of the BAS assessments (**Table 81**).

Table 81: Summary of Barnes Akathisia Global Assessment Score

	PBO (N=86) n/N (%)	LTG (N=87) n/N (%)	LTG VS PBO CHI-SQUARE P-VALUE
Baseline (OL Phase)			
n		298	
Absent		249/298 (84%)	
Questionable		39/298 (13%)	
Mild akathisia		8/298 (3%)	
Moderate akathisia		2/298 (<1%)	
Marked akathisia		0/298	
Severe akathisia		0/298	
OL Week 18/ Early Withdrawal			
n		279	
Absent		260/279 (93%)	
Questionable		14/279 (5%)	
Mild akathisia		3/279 (1%)	
Moderate akathisia		2/279 (<1%)	
Marked akathisia		0/279	
Severe akathisia		0/279	
Randomization Week 36/ Early Withdrawal			
n	83	83	0.555
Absent	77/83 (93%)	76/83 (92%)	
Questionable	5/83 (6%)	6/83 (7%)	
Mild akathisia	0/83	1/83 (1%)	
Moderate akathisia	1/83 (1%)	0/83	
Marked akathisia	0/83	0/83	
Severe akathisia	0/83	0/83	

Source: Clinical Study Report; SCA 102833, Table 29.4, pages 1841.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As would be expected with a shorter phase, fewer subjects reported AEs in the OL Taper Phase (40%) compared with the OL Phase (83%), as shown in **Table 82** below.

Table 82: Summary of Adverse Events with Onset in the OL Phase and OL Taper Phase – An Overview (OL and OL Taper ITT Population)

	OL (N=298)	OL Taper (N=35)
Any AE, n (%)	**247 (83)**	**14 (40)**
AEs leading to study discontinuation	26 (9)	0
AEs related to study treatment	88 (30)	2 (6)
AEs leading to dose reduction	8 (3)	1 (3)
AEs leading to dose interruption/delay	8 (3)	0
Possible Suicidality-related AE	20 (7)	2 (6)
Dermatological/Hypersensitivity AE	39 (13)	1 (3)
Any SAE, n (%)	**18 (6)**	**1 (3)**
SAEs related to study treatment	5 (2)	0
Fatal SAEs	0	0
Fatal SAEs related to study treatment	0	0

Note: Subjects can be included in more than one category.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 35, page 101.

Similarly, as would be expected with a shorter phase, fewer subjects reported AEs in the Double-blind Taper Phase compared to the Randomized Phase for both treatment groups, as shown in **Table 83** below. Overall, the incidence of AEs was similar between treatment groups. In the Randomized Phase, PSRAEs and dermatological AEs were reported more frequently in the LTG group compared with the PBO group (see **Section 7.3.4** above).

Table 83: Summary of Adverse Events with Onset in the Randomized Phase and Double-blind Taper Phase – An Overview (Randomized and Double-blind Taper ITT Population)

	Randomized		Double-blind Taper	
	PBO (N=86)	LTG (N=87)	PBO (N=55)	LTG (N=53)
Any AE, n (%)	**64 (74)**	**66 (76)**	**14 (25)**	**18 (34)**
AEs leading to study discontinuation	25 (29)	18 (21)	1 (2)	0
AEs related to study treatment	13 (15)	16 (18)	0	2 (4)
AEs leading to dose reduction	1 (1)	0	0	0
AEs leading to dose interruption/delay	0	3 (3)	0	0
Possible Suicidality-related AE	1 (1)	6 (7)	2 (4)	1 (2)
Dermatological/Hypersensitivity AE	3 (3)	8 (9)	0	2 (4)
Any SAE, n (%)	**3 (3)**	**1 (1)**	**2 (4)**	**0**
SAEs related to study treatment	0	0	0	0
Fatal SAEs	0	0	0	0
Fatal SAEs related to study treatment	0	0	0	0

Note: Subjects can be included in more than one category.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 36, page 101

Overall, in the OL phase, the incidence of AEs was similar between age subgroups within each phase, as shown in **Table 84** below.

Table 84: Summary of Adverse Events by Age with Onset in the OL Phase and OL Taper Phase – An Overview (OL and OL Taper ITT Population)

	OL		OL Taper	
	10-12 yrs (N=117)	13-17 yrs (N=181)	10-12 yrs (N=16)	13-17 yrs (N=19)
Any AE, n (%)	96 (82)	151 (83)	6 (38)	8 (42)
AEs leading to study discontinuation	10 (9)	16 (9)	0	0
AEs related to study treatment	32 (27)	56 (31)	0	2 (11)
AEs leading to dose reduction	1 (<1)	7 (4)	0	1 (5)
AEs leading to dose interruption/delay	4 (3)	4 (2)	0	0
Possible Suicidality-related AE	9 (8)	11 (6)	1 (6)	1 (5)
Dermatological/Hypersensitivity AE	18 (15)	21 (12)	0	15)
Any SAE, n (%)	**7 (6)**	**11 (6)**	**0**	**1 (5)**
SAEs related to study treatment	2 (2)	3 (2)	0	0
Fatal SAEs	0	0	0	0
Fatal SAEs related to study treatment	0	0	0	0

Note: Subjects can be included in more than one category.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 37, page 102

As would be expected with a shorter phase, fewer subjects reported AEs in the Double-blind Taper Phase compared to the Randomized Phase for both treatment and age groups, as shown in **Table 85** below. In the Randomized Phase, the incidence of withdrawal due to an AE within a treatment group was similar between age groups. Overall, in the Randomized Phase, the incidence of AEs was similar between treatment groups within each phase with the exception of PSRAEs and dermatological AEs which were higher in the LTG groups.

In the Randomized Phase, PSRAEs and dermatological AEs were reported more frequently in the LTG group compared with the PBO group regardless of age. Additionally, PSRAEs were reported at a higher incidence in the 10-12 year-old LTG subgroup (9%) compared to the 13-17 year-old LTG subgroup (6%). Dermatological AEs were reported at a higher incidence in the 10-12 year-old LTG subgroup (15%) compared to the 13-17 year-old LTG subgroup (6%). See **Section 7.3.4** for further details.

Table 85: Summary of Adverse Events by Age and Treatment Group with Onset in the Randomized Phase – An Overview (Randomized and Double-blind Taper ITT Population)

	Randomized				Double Blind Taper			
	PBO 10-12 yrs (N=33)	LTG 10-12 yrs (N=33)	PBO 13-17 yrs (N=53)	LTG 13-17 yrs (N=54)	PBO 10-12 yrs (N=22)	LTG 10-12 yrs (N=21)	PBO 13-17 yrs (N=33)	LTG 13-17 yrs (N=32)
Any AE, n (%)	**27 (82)**	**27 (82)**	**37 (70)**	**39 (72)**	**5 (23)**	**4 (19)**	**9 (27)**	**14 (44)**
AEs leading to permanent discontinuation of study treatment	9 (27)	7 (21)	15 (28)	11 (20)	0	0	1 (3)	0
AEs leading to study discontinuation	10 (30)	7 (21)	15 (28)	11 (20)	0	0	1 (3)	0
AEs related to study treatment	7 (21)	8 (24)	6 (11)	8 (15)	0	0	0	2 (6)
AEs leading to dose reduction	0	0	1 (2)	0	0	0	0	0
AEs leading to dose interruption/delay	0	1 (3)	0	2 (4)	0	0	0	0
Possible Suicidality-related AE	0	3 (9)	1 (2)	3 (6)	0	1 (5)	2 (6)	0
Dermatological/Hypersensitivity AE	1 (3)	5 (15)	2 (4)	3 (6)	0	0	0	2 (6)
Any SAE, n (%)	1 (3)	1 (3)	2 (4)	0	1 (5)	0	1 (3)	0
SAEs related to study treatment	0	0	0	0	0	0	0	0
Fatal SAEs	0	0	0	0	0	0	0	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0

Note: Subjects can be included in more than one category.
Electronically copied and reproduced from sponsor's submission: Clinical Study Report; SCA 102833, Table 38, page 103

The most common (reported in ≥5% of subjects) AEs in the OL Phase and OL Taper Phase are summarized in **Table 86** below. In the OL Phase, the system organ classes (SOCs) with a ≥20% incidence of AEs included nervous system disorders (41%), gastrointestinal disorders (35%), infections and infestations (30%), respiratory, thoracic and mediastinal disorders (24%), and psychiatric disorders (23%). In the OL Phase, AEs reported in ≥10% of subjects were headache (34%), abdominal pain upper (16%), nausea (13%), and oropharyngeal pain (10%). In the OL Taper Phase, 14 (40%) subjects reported AEs. AEs reported in ≥5% of subjects in the OL Taper Phase included headache (20%), somnolence (6%) and suicidal ideation (6%). All other AEs were reported in <5% of subjects.

Table 86: Summary of Common Adverse Events (≥5% of Subjects) with Onset in Either the OL or OL Taper Phase (OL and OL Taper ITT Population)

Preferred Term	OL Phase	OL Taper Phase
	LTG (N=298)	LTG (N=35)
Any event, n (%)	247 (83)	14 (40)
Headache	102 (34)	7 (20)
Abdominal pain upper	47 (16)	1 (3)
Nausea	39 (13)	0
Oropharyngeal pain	30 (10)	0
Vomiting	25 (8)	0
Nasopharyngitis	25 (8)	0
Dizziness	24 (8)	0
Diarrhea	23 (8)	1 (3)
Insomnia	23 (8)	0
Cough	21 (7)	0
Suicidal ideation	19 (6)	2 (6)
Irritability	18 (6)	0
Fatigue	17 (6)	0
Influenza	14 (5)	0
Sinusitis	14 (5)	0
Somnolence	11 (4)	2 (6)

Source: Clinical Study Report; SCA 102833, Tables 39 (pages 104-105) and 22.7 (pages 1652-1653)

The most common (reported in ≥5% of subjects) AEs in the Randomized Phase are summarized in **Table 87** below. The SOCs with a ≥20% incidence of AEs in either treatment group included infections and infestations (PBO=22%, LTG=28%), psychiatric disorders (PBO=20%, LTG=28%), nervous system disorders (PBO=22%, LTG=22%), general disorders and administration site conditions (PBO=23%, LTG=17%), respiratory, thoracic and mediastinal disorders (PBO=19%, LTG=21%), and gastrointestinal disorders (PBO=8%, LTG=20%).

In the Randomized Phase, the Overall number and types of AEs reported was similar between treatment groups. Exceptions (AEs that differed by more than 5% between groups) included influenza (PBO=2%, LTG=8%), irritability (PBO=16%, LTG=8%), oropharyngeal pain (PBO=2%, LTG=8%), and sinus congestion (PBO=5%, LTG=0).

Table 87: Summary of Common Adverse Events (≥5% of Subjects in Either Treatment Group) with Onset in Randomized Phase

Preferred Term	PBO (N=86)	LTG (N=87)
Any event, n (%)	64 (74)	66 (86)
Headache	17 (20)	15 (17)
Influenza	2 (2)	7 (8)
Irritability	14 (16)	7 (8)
Oropharyngeal pain	2 (2)	7 (8)
Nasal Congestion	6 (7)	6 (7)
Insomnia	5 (6)	6 (7)
Cough	4 (5)	6 (7)
Nasopharyngitis	4 (5)	5 (6)
Vomiting	2 (2)	5 (6)
All Mania	7 (8)	5 (6)
Dermatitis contact	2 (2)	4 (5)
Abdominal pain upper	1 (1)	4 (5)
Suicidal ideation	0	4 (5)
Upper Respiratory Tract Infection	4 (5)	3 (3)
Dizziness	4 (5)	2 (2)
Pyrexia	5 (6)	2 (2)
Sinus congestion	4 (5)	0

Source: Clinical Study Report; SCA 102833, Table 40, page 106-107

In the Double-Blind Taper Phase, 18 (34%) subjects in the LTG group and 14 (25%) subjects in the PBO group reported AEs. Headache was the only AE reported in ≥5% (8% in the LTG group and 7% in the PBO group). All other AEs were reported in <5% of subjects.

In the OL Phase, All Rash and was reported in <5% of subjects. In the Randomized Phase, All Rash was reported in <5% of subjects in any treatment group (**Table 88)**.

Table 88: Summary of "All Rash*" Adverse Events with Onset in OL and in Randomized Phases by Treatment Group [n (%)]

Preferred Term	OL Phase	Randomized Phase	
	LTG (N=298)	PBO (N=86)	LTG (N=87)
All Rash*	11 (4)	1 (1)	2 (2)
-Rash	6 (2)	1 (1)	2 (2)
-Dermatitis	1 (<1)	0	0
-Dermatitis allergic	1 (<1)	0	0
-Purpura	1 (<1)	0	0
-Rash generalized	1 (<1)	0	0
-Rash papular	1 (<1)	0	0

*All Rash included the following verbatim terms: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.
Source: Clinical Study Report; SCA 102833, Table 39, page 104-105 and Table 40, page 106-107

In the OL Phase, All Mania was reported in <5% of subjects. In the Randomized Phase, All Mania was reported in 8% of subjects in the PBO group compared to 6% in the LTG treatment group (**Table 89**).

Table 89: Summary of "All Mania*" Adverse Events with Onset in OL and in Randomized Phases by Treatment Group [n (%)]

Preferred Term	OL Phase	Randomized Phase	
	LTG (N=298)	PBO (N=86)	LTG (N=87)
All Mania*	6 (2)	7 (8)	5 (6)
-Mania	4 (1)	5 (6)	3 (3)
-Bipolar I disorder	2 (<1)	2 (2)	1 (1)
-Bipolar disorder	0	2 (2)	4 (5)

*All Mania included the following verbatim terms: bipolar I- worsening (self-harm)- mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, worsening manic symptoms.

There were no seizures reported in the OL Phase or Randomized Phase.

Adverse Events by Age

In the OL Phase, the types and incidence of AEs were similar between age groups (**Table 90**). AEs that differed by more than 5% between groups included nausea (18%) and insomnia (10%) in the 13-17 year-old subgroup compared with the 10-12 year-old subgroup (nausea=6%, insomnia=4%). The incidence of all other events was similar

regardless of age subgroup. In the OL Taper Phase in the 10-12 year-old subgroup, a total of 6/16 (38%) subjects reported AEs. Headache was the only AE reported in more than 1 subject (3/16[19%]). In the 13-17 year-old subgroup, a total of 8/19 (42%) subjects reported an AE. Headache (4/19[21%]) and somnolence (2/19[11%]) were the only AEs reported in more than a single subject.

Table 90: Summary of Common Adverse Events (Reported in ≥5% of Subjects) by Age with Onset in OL Phase

Preferred Term	10-12 yrs (N=117)	13-17 yrs (N=181)
Any event, n (%)	**96 (82)**	**151 (83)**
Headache	38 (32)	64 (35)
Nausea	7 (6)	32 (18)
Abdominal pain upper	17 (15)	30 (17)
Nasopharyngitis	7 (6)	18 (10)
Oropharyngeal pain	12 (10)	18 (10)
Insomnia	5 (4)	18 (10)
Dizziness	7 (6)	17 (9)
Vomiting	9 (8)	16 (9)
Diarrhoea	7 (6)	16 (9)
Cough	6 (5)	15 (8)
Fatigue	5 (4)	12 (7)
Sinusitis	3 (3)	11 (6)
Suicidal ideation	8 (7)	11 (6)
Irritability	7 (6)	11 (6)
Dyspepsia	1 (<1)	9 (5)
Upper respiratory tract infection	1 (<1)	9 (5)
Decreased appetite	4 (3)	9 (5)
Influenza	6 (5)	8 (4)
Agitation	6 (5)	7 (4)
Pyrexia	7 (6)	6 (3)
Somnolence	7 (6)	4 (2)
Pharyngitis streptococcal	7 (6)	3 (2)

Note: AEs are ordered by decreasing frequency in the 13-17 year-old group.
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In the Randomized Phase, the incidence of AEs was higher in the 10-12 year-old group (82%) compared to the 13-17 year-old group (~71%), as shown in **Table 91** below. The overall incidence of AEs was similar between PBO and LTG within each age group. AEs that were more than 5% higher between LTG groups included headache (21%), irritability (15%), cough (12%), suicidal ideation (9%), dermatitis contact (9%), excoriation (95), rhinorrhea (6%), and pyrexia (6%) in the 10-12 year-old LTG group compared with the 13-17 year-old LTG group while the incidence of anxiety (6%) and

agitation (6%) was higher in the 13-17 year-old LTG groups compared to the 10-12 year-old LTG group. All other events were similar regardless of treatment or age group.

Table 91: Summary of Common Adverse Events (Reported in ≥5% of Subjects) by Age with Onset in Randomized Phase

	10-12 yrs		13-17 yrs	
Preferred Term	PBO N=33	LTG N=33	PBO N=53	LTG N=54
ANY EVENT, n (%)	**27 (82)**	**27 (82)**	**37 (70)**	**39 (72)**
Headache	6 (18)	7 (21)	11 (21)	8 (15)
Influenza	0	2 (6)	2 (4)	5 (9)
Oropharyngeal pain	0	2 (6)	2 (4)	5 (9)
Insomnia	1 (3)	2 (6)	4 (8)	4 (7)
Nasal congestion	2 (6)	2 (6)	4 (8)	4 (7)
Anxiety	0	0	0	3 (6)
Vomiting	2 (6)	2 (6)	0	3 (6)
Agitation	1 (3)	0	0	3 (6)
Upper respiratory tract infection	0	1 (3)	4 (8)	2 (4)
Irritability	3 (9)	5 (15)	11 (21)	2 (4)
Nasopharyngitis	1 (3)	3 (9)	3 (6)	2 (4)
Cough	2 (6)	4 (12)	2 (4)	2 (4)
Abdominal pain upper	1 (3)	2 (6)	0	2 (4)
Dermatitis contact	0	3 (9)	2 (4)	1 (2)
Gastroenteritis viral	0	2 (6)	0	1 (2)
All Mania*	3 (9)	3 (9)	4 (8)	2 (4)
-Mania	3 (9)	2 (6)	2 (4)	1 (2)
-Bipolar I disorder	0	1 (3)	2 (4)	1 (2)
-Bipolar disorder	0	1 (3)	0	0
Aggression	2 (6)	1 (3)	1 (2)	1 (2)
Suicidal ideation	0	3 (9)	0	1 (2)
Dizziness	0	1 (3)	4 (8)	1 (2)
Pyrexia	2 (6)	2 (6)	3 (6)	0
Rhinorrhoea	1(3)	2 (6)	0	0
Sinus congestion	2 (6)	0	2 (4)	0
Excoriation	1 (3)	3 (9)	0	0

Note: AEs are ordered by decreasing frequency in the 13-17 year-old group.

*All Mania included the following verbatim terms: bipolar I- worsening (self-harm)- mood state mixed, worsening bipolar mania, worsening bipolar I disorder-mixed type disorder, worsening of bipolar symptoms (mania), worsening of bipolar symptoms (mixed episode: depression and mania), worsening of bipolar symptoms (mixed), hospitalization for worsening bipolar disorder, hospitalization for manic symptoms, increase in mania, increased manic behaviors, mania, manic episode, worsening mania, worsening manic symptoms. All Rash included the following verbatim terms: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.

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Drug-related AEs

In the OL Phase, 30% of subjects reported an AE that was considered by the investigator to be possibly related to LTG (**Table 92**). Headache (8%) was the only AE reported in ≥5% of subjects. All other possibly drug-related AEs were reported by ≤3% of subjects. In the OL Taper Phase, 2 (6%) subjects reported drug-related AEs (visual impairment, headache).

Table 92: Summary of Possibly Drug Related Adverse Events (≥2% of Subjects) with Onset in OL Phase

Preferred Term	LTG (N=298)
Any event, n (%)	**88 (30)**
Headache	24 (8)
Nausea	10 (3)
Abdominal pain upper	9 (3)
Decreased appetite	8 (3)
Fatigue	8 (3)
Irritability	8 (3)
Dizziness	7 (2)
Somnolence	7 (2)
Diarrhoea	7 (2)
Agitation	6 (2)
Insomnia	5 (2)
All Rash*	5 (2)
-Rash	2 (<1)
-Dermatitis allergic	1 (<1)
-Purpura	1 (<1)
-Rash generalized	1 (<1)

All Rash included the following verbatim terms: rash-upper abdomen, hypersensitivity and rash, skin rash (purpura), rash, rash (skin irritation) on upper right arm, rash on chest and L armpit, rash on chest and legs, rash on tops of both thighs and inner left forearm, all over body rash, and papular rash.

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For the Randomized Phase, AEs considered by the investigator to be possibly related to investigational product were similar in incidence and types between treatment groups (**Table 93**). AEs of headache and irritability were reported by ≥2% of subjects in either treatment group. There were 2 drug-related AEs in the Double-blind Taper Phase, both in the LTG group (nasopharyngitis in one subject and agitation in another subject).

Table 93: Summary of Possibly Drug Related Adverse Events (≥2% of Subjects in Either Treatment Group) with Onset in Randomized Phase

Preferred Term	PBO (N=86)	LTG (N=87)
Any event, n (%)	**13 (15)**	**16 (18)**
Headache	4 (5)	2 (2)
Irritability	3 (3)	2 (2)
Agitation	0	2 (2)

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Drug-related AEs by Age

In the OL Phase, the types and incidence of drug-related AEs were similar between age groups (**Table 94**). None of the AEs differed by more than 5% between age groups.

In the OL Taper Phase in the 13-17 year-old subgroup, a total of 2/19 (11%) subjects reported drug-related AEs (visual impairment, headache). No drug-related AEs were reported in the 10-12 year-old subgroup.

Table 94: Summary of Common Possibly Drug Related Adverse Events (≥2% of Subjects in Either Group) with Onset in OL Phase

Preferred Term	10-12 yrs (N=117)	13-17 yrs (N=181)
Any event, n (%)	**32 (27)**	**56 (31)**
Headache	10 (9)	14 (8)
Nausea	1 (<1)	9 (5)
Fatigue	2 (2)	6 (3)
Irritability	2 (2)	6 (3)
Dizziness	2 (2)	5 (3)
Agitation	1 (<1)	5 (3)
Decreased appetite	3 (3)	5 (3)
Abdominal pain upper	5 (4)	4 (2)
Increased appetite	2 (2)	2 (1)
Insomnia	1 (<1)	4 (2)
Tremor	0	4 (2)
Diarrhea	3 (3)	4 (2)
Somnolence	5 (4)	2 (1)
Vomiting	2 (2)	1 (<1)
Weight increased	2 (2)	0
Dyspnoea	2 (2)	0

Note: AEs are ordered by decreasing frequency in the 13-17 year-old group.
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For the Randomized Phase, AEs considered by the Investigator to be possibly related to investigational product were similar in incidence and types between treatment groups and within age subgroups (**Table 95**). However, more drug-related AEs were reported in the 10-12 year-old subgroup compared to the 13-17 year-old subgroup. There were 2 (6%) drug-related AEs in the Double-blind Taper Phase (nasopharyngitis, agitation). Both received LTG and were in the 13-17 year-old subgroup.

Table 95: Summary of Common Possibly Drug Related Adverse Events (More than One Subject in Any Treatment Group) with Onset in Randomized Phase

	10-12 yrs		13-17 yrs	
Preferred Term	PBO (N=33)	LTG (N=33)	PBO (N=53)	LTG (N=54)
Any event, n (%)	**7 (21)**	**8 (24)**	**6 (11)**	**8 (15)**
Headache	1 (3)	0	3 (6)	2 (4)
Irritability	1 (3)	2 (6)	2 (4)	0
Agitation	0	0	0	2 (4)

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7.4.2 Laboratory Findings

Hematology and Clinical Chemistry

There were no meaningful differences between groups for mean hematology or chemistry values at baseline. There were no changes from screen in the OL Phase of clinical significance. In the Randomized Phase, changes from baseline were similar between LTG and PBO groups, and there were no changes of clinical significance. Furthermore, in the OL Phase, hematology and chemistry values remained generally consistent with no clinically significant changes over time. In the Randomized Phase, hematology and chemistry values remained generally consistent in both groups with no clinically significant changes over time or differences between LTG and PBO groups.

In the case of significant abnormalities, the laboratory contacted the investigator and relevant GSK personnel by telephone. Phone alert criteria are provided in Table **96** below.

Table 96: Phone Alert Values for Laboratory Assessments

	Exclusion			Alert Value	
	CONVENTIONAL	*SI UNITS*		*CONVENTIONAL*	*SI UNITS*
ALT (SGPT)	>67	>67		>90 (3-12y)	>90 (3-12y)
	>72	>72		>96 (13+y)	>96 (13+y)
AST (SGOT)	>63	>63		>126	>126
Bilirubin, Total	>1.9	>32		>2.6	>44
Bilirubin, Direct	>0.6	>10			
TSH	<0.40 or >5.50	<0.40 or >5.50		<0.30 or >6.0	<0.30 or >6.0
Sodium				<125 or >155	<125 or >155
Potassium				<3.0 or >6.5	<3.0 or >6.5
Glucose				<40 or >350	<2.2 or >19.4
Creatinine				>1.5 (3-12y)	133 (3-12y)
				>2.1 (13+y)	186 (13+y)
Blood Alcohol	>0.009	>0.009			
Hemoglobin					
Platelet				<31,000 or >1,499,000	<31 or >1499

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In the OL Phase, changes in laboratory values with respect to the telephone alert ranges were not reported in any subjects. There were 4 events in the PBO group and 4 events in the LTG group that met these criteria in the Randomized Phase, as shown in **Table 97** below.

Table 97: Summary of Laboratory Values with Respect to Telephone Alert Ranges at Any time during the Randomized Phase (ITT Randomized Phase)

n	Baseline Category	High	Normal	Low	Total
PBO					
Alanine Transferase					
83	High	0	0	0	0
	Normal	1 (1)	83 (100)	0	83 (100)
	Low	0	0	0	0
	Missing	0	0	0	0
	Total	1 (1)	83 (100)	0	83 (100)
Glucose					
83	High	0	0	0	0
	Normal	0	83 (100)	1 (1)	83 (100)
	Low	0	0	0	0
	Missing	0	0	0	0
	Total	0	83 (100)	1 (1)	83 (100)
Potassium					
83	High	0	0	0	0
	Normal	1 (1)	83 (100)	0	83 (100)
	Low	0	0	0	0
	Missing	0	0	0	0
	Total	1 (1)	83 (100)	0	83 (100)
Thyroid Stimulating Hormone					
83	High	0	0	0	0
	Normal	0	83 (100)	1 (1)	83 (100)
	Low	0	0	0	0
	Missing	0	0	0	0
	Total	0	83 (100)	1 (1)	83 (100)
LTG					
Thyroid Stimulating Hormone					
83	High	0	0	0	0
	Normal	2 (2)	83 (100)	2 (2)	83 (100)
	Low	0	0	0	0
	Missing	0	0	0	0
	Total	2 (2)	83 (100)	2 (2)	83 (100)

Note: a subject can be included in more than one category.
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Hepatic Enzymes

When subjects met the following liver chemistry threshold criteria, investigational product must have been permanently withdrawn, additional testing performed, and the subject monitored until the tests stabilized or returned to baseline values.

The subject was to be permanently withdrawn if:

- ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (>35% direct).
- ALT ≥ 5xULN.
- ALT ≥ 3xULN if associated with the appearance or worsening of hepatitis symptoms or rash.

There were no subjects that had liver function tests (LFTs) meeting the stopping criteria in either phase of the trial. No subjects required liver biopsy. There were few LFT shifts from normal to high in the OL Phase or the Randomized Phase.

7.4.3 Vital Signs

The criteria in **Table 98** below were used in the trial to define significant changes in vital signs:

Table 98: Vital Signs Significant Change Thresholds [Baseline (OL) or Randomization (RAND)]

Variable		Age 10-12	Age 13-17
SBP	Significant increase	SBP ≥125 mmHg and increase of ≥ 20 mmHg	SBP ≥130 mmHg and increase of ≥ 20
	Significant decrease	SBP ≤85 mmHg and decrease of ≥ 20 mmHg	SBP ≤90 mmHg and decrease of ≥ 20 mmHg
DBP	Significant increase	DBP ≥80 mmHg and increase of ≥ 20 mmHg	DBP ≥80 mmHg and increase of ≥ 20 mmHg
	Significant decrease	DBP ≤45 mmHg and decrease of ≥ 20 mmHg	DBP ≤50 mmHg and decrease of ≥ 20
Heart Rate	Significant increase	HR ≥120 bpm and increase of ≥ 30 bpm	HR ≥110 bpm and increase of ≥ 30 bpm
	Significant decrease	HR ≤60 bpm and decrease of ≥ 30 bpm	HR ≤55 bpm and decrease of ≥ 30 bpm
Weight	Increase and or decrease	+/- 7%	+/- 7%

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Table 99 summarizes the number of subjects with clinically significant threshold changes in vital signs and weight during the OL and Randomized Phases. **Table 100**

summarizes the number of subjects with clinically significant threshold changes in vital signs and weight during the Taper Phases. In the OL Phase, there were no clinically meaningful changes in vital signs. In the Randomized Phase, there were no clinically significant differences between treatment groups in vital signs during the trial.

Sporadic findings of elevated SBP, DBP, and HR that were considered clinically significant per pre-defined thresholds were observed during the OL and Randomized Phase. However, review of the individual cases showed these were not persistent and resolved.

Mean change from baseline for BMI in the OL Phase was not notable. No differences were observed in mean change from randomization in BMI. Mean change in BMI during the Randomized Phase ranged from -1.063 (Week 1) to 0.635 (at the end of the Double-Blind Taper) for the LTG group, and -0.060 (Week 3) to 0.695 (at the end of the Double-Blind Taper) for the PBO group.

Significant changes (±7%) in weight were observed in the Randomized and Double-Blind Taper Phases. Significant decreases and increases were observed at a similar incidence regardless of phase or treatment group.

Table 99: Summary of Clinically Significant Threshold Changes in Vital Signs and Weight (OL and Randomized ITT Population)

	OL ITT	Randomized ITT		
	LTG (N=298)	PBO (N=86)	LTG (N=87)	Total (N=173)
Diastolic BP (mmHg), n (%)				
Significant Decrease	1 (<1)	0	0	0
Significant Increase	22 (7)	5 (6)	8 (9)	13 (8)
Systolic BP (mmHg), n (%)				
Significant Decrease	4 (1)	3 (3)	4 (5)	7 (4)
Significant Increase	38 (13)	8 (9)	14 (16)	22 (13)
Heart Rate (bpm), n (%)				
Significant Decrease	7 (2)	2 (2)	0	2 (1)
Significant Increase	5 (2)	0	4 (5)	4 (2)
Weight (kg), n (%)				
Significant Decrease	17 (6)	9 (10)	9 (10)	18 (10)
Significant Increase	40 (13)	35 (41)	36 (41)	71 (41)

Note: Changes were counted from baseline (randomization) visit to any time during OL (randomization) phase. The threshold criteria are age specific.
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Table 100: Summary of Clinically Significant Threshold Changes in Vital Signs and Weight (OL and Double-blind Taper Phases, ITT Population)

	OL Taper		Randomized Taper	
	LTG (N=35)	PBO (N=55)	LTG (N=53)	Total (N=108)
Diastolic BP (mmHg), n (%)				
Significant Decrease	0	0	0	0
Significant Increase	2 (6)	4 (7)	4 (8)	8 (7)
Systolic BP (mmHg), n (%)				
Significant Decrease	1 (3)	0	0	0
Significant Increase	5 (14)	5 (9)	8 (15)	13 (12)
Heart Rate (bpm), n (%)				
Significant Decrease	0	0	0	0
Significant Increase	0	0	2 (4)	2 (2)
Weight (kg), n (%)				
Significant Decrease	1 (3)	4 (7)	0	4 (4)
Significant Increase	5 (14)	24 (44)	21 (40)	45 (42)

Note: Changes were counted from baseline visit to any time during OL Taper and from randomization for the Double-blind Taper.
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7.4.4 Electrocardiograms (ECGs)

The sponsor has provided extensive criteria applied for clinically significant changes in ECG as shown in **Table 101** below:

Table 101: ECG Significant Abnormality Criteria

	ECG CRITERION VALUE	
	ABNORMAL INSIGNIFICANT	ABNORMAL SIGNIFICANT
RHYTHM		
Sinus Tachycardia	100 bpm < HR < 120bpm	≥ 120 bpm
Sinus Bradycardia	40 bpm ≤ HR < 50bpm	< 40 bpm
Sinus Pause/Arrest	1. 5 to 3. 0 seconds	> 3. 0 seconds
Atrial premature complex	2 beats if unifocal	2 beats if multifocal/bi or trigeminy/ couplets/ ≥3 beats
Ventricular premature complex	2 beats, if unifocal	2 beats if multifocal/bi or trigeminy/ couplets/ ≥3 beats
Supraventricular Tachycardia	None	Any
Ventricular Tachycardia	None	Any
Atrial Fibrillation	None	Any
Atrial Flutter	None	Any
Ectopic Atrial Rhythm	All	None
Junctional Rhythm	None	Any
Idioventricular Rhythm	None	Any
AXIS		
Left Axis Deviation	-45°< QRS axis < -30°	QRS axis ≤ -45°/LAHB
Right Axis Deviation	90° < QRS axis < 120°	QRS axis ≥120°/LPHB
CONDUCTION		
1st degree A-V Block	200 ms ≤ PR < 210 ms	PR ≥ 210 ms
2nd degree A-V Block	None	All
3rd degree A-V Block	None	All
LSBB	None	All
RBBB	None	All
ICRBBB (QRS<120 ms)	All	None
Short PR/Preexcitation syndrome	PR <120 ms	Delta wave + PR <120 ms
Other Intra-ventricular Conduction delay	110 ms ≤ QRS < 120 ms	QRS ≥ 120 ms
LONG QTcF (Fridericia)		
	450 ms < QTc ≤ 500 ms and not satisfying criteria for algorithm	QTc > 450 ms plus increase of 30 ms from Baseline OR QTc > 500 ms
Uncorrected QT(All)	None	> 500 ms
U Wave Abnormal U Wave	None	All
ENLARGEMENT/ HYPERTROPHY		
Atrial abnormalities	Borderline	Definite
Ventricular abnormalities		Voltage criteria plus Abnormal repolarization
MYOCARDIAL INFARCTION		
Acute or Recent Old or Age Indeterminate	None None	Any All
ST/T MORPHOLOGY		
ST elevation suggestive of Myocardial Injury	None	In 2 or more contiguous leads
ST depression suggestive of Myocardial Ischemia	None	In 2 or more contiguous leads
T wave Inversions suggestive of Myocardial Ischemia	None	In 2 or more contiguous leads
Non-specific ST and or T Wave abnormalities	In 2 or more leads	None
PACEMAKER	None	All

ECG Significant Abnormality Criteria (continued)

		BASELINE ECG CRITERION VALUE		FOLLOW-UP ECG CRITERION VALUE	
		ABNORMAL		ABNORMAL	
		INSIGNIFICANT	SIGNIFICANT	INSIGNIFICANT	SIGNIFICANT
RHYTHM					
Sinus Tachycardia	≤12years	110bpm < HR ≤ 130bpm	HR >130 bpm	110 < HR ≤ 130 bpm	> 130 + increase of ≥ 15bpm
	>12years	105bpm < HR ≤ 120bpm	HR >120 bpm	105 < HR ≤ 120 bpm	> 120 + increase of ≥ 15bpm
Sinus Bradycardia	≤ 12years	45 bpm < HR < 55bpm	HR ≤ 45 bpm	45 < HR < 55 bpm	≤ 45 + decrease of > 5bpm
	> 12years	40 bpm < HR < 50bpm	HR ≤ 40 bpm	40 < HR < 50 bpm	≤ 40 + decrease of > 5bpm
Atrial premature complex		2 beats, if unifocal	2 beats, if multifocal or ≥ 3 beats or Couplets	2 beats, if unifocal	2 beats, if multifocal or ≥ 3 beats or Couplets
Ventricular premature complex		2 beats, if unifocal	2 beats, if multifocal or ≥ 3 beats or Couplets	2 beats, if unifocal	2 beats, if multifocal or ≥ 3 beats or Couplets
Supraventricular Tachycardia		None	All	None	All
Ventricular Tachycardia		None	All	None	All
Atrial Fibrillation		None	All	None	All
Atrial Flutter		None	All	None	All
Ectopic/Low Atrial Rhythm		All	None	All	None
AXIS					
Left Axis Deviation		-30°< QRS axis ≤ -10°	QRS axis ≤ -30°/ (LAHB)	-30°< QRS axis ≤ -10°	≤ -30° plus decrease of ≥15°
Right Axis Deviation		110° < QRS axis < 125°	QRS axis ≥125°/ (LPHB)	110° < QRS axis < 125°	≥ 125° plus increase of ≥15° (Hemiblocks are always Sig.)
CONDUCTION					
1st degree A-V Block					
≤ 12years		170 ms ≤ PR < 180 ms	PR ≥ 180 ms	PR ≥ 180 ms	PR ≥ 180 ms + increase of 20 ms
> 12years		180 ms ≤ PR < 190 ms	PR ≥ 190 ms	PR ≥ 190 ms	PR ≥ 190 ms + increase of 20 ms
2nd degree A-V Block		None	All	None	All
3rd degree A-V Block		None	All	None	All
LBBB	≤ 12 years (QRS > 100)	None	All	None	All
	> 12 years (QRS > 110)	None	All	None	All
RBBB	≤ 12 years (QRS > 100)	None	All	None	All
	> 12 years (QRS > 110)	None	All	None	All
ICRBBB					
	≤ 12 years (90 < QRS ≤ 100)	All	None	All	None
	> 12 years (100 < QRS ≤ 110)	All	None	All	None
Short PR Syndrome		PR ≤ 100 ms	WPW (PR≤100ms+Δwave)	PR ≤ 100 ms	WPW (PR≤100 ms+Δwave)
Other Intra-ventricular Conduction Delay					
≤ 12 years		90 ms ≤QRS <100 ms	QRS ≥ 100 ms	QRS ≥ 90 ms and not and not satisfying criteria for Significant	≥100 ms+increase of ≥ 20ms
> 12 years		100 ms ≤QRS <110 ms	QRS ≥ 110 ms	QRS ≥ 100 ms and not satisfying criteria for Significant	≥110 ms+increase of ≥20 ms
Long QTc (Fridericia)			QTc > 450 ms	450ms <QTc ≤ 500ms and not satisfying criteria for Significant	QTc > 450 ms plus increase of ≥ 30 ms from Baseline OR QTc > 500 ms
Uncorrected QT			QT > 500ms		QT > 500ms
Abnormal U Wave		None	All	None	All
HYPERTROPHY					
Right Atrial Hypertrophy		None	P wave amplitude in lead II > 2.5 mm if HR ≤ 100 OR > 3 mm if HR > 100	None	P wave amplitude in lead II > 2.5 mm if HR ≤ 100 OR > 3 mm if HR > 100
Left Atrial Hypertrophy		None	P wave duration > 120 ms in Lead II	None	P wave duration > 120 ms in Lead II
Right Ventricular Hypertrophy		None		None	
≤ 12 years			R wave Height > 12mm or R:S ratio in V1 > 2 + Right axis deviation/ Strain Pattern		R wave Height > 12mm or R:S ratio in V1 > 2 + Right axis deviation/ Strain Pattern
> 12 years			R wave Height > 10mm or R:S ratio in V1 > 2 + Right axis deviation/ Strain Pattern		R wave Height > 10mm or R:S ratio in V1 > 2 + Right axis deviation/ Strain Pattern

ECG Significant Abnormality Criteria (continued)

Left Ventricular Hypertrophy				
≤ 12 years	None	Sin V1 > 25 mm + Strain Pattern	None	Sin V1 > 25 mm + Strain Pattern
> 12 years		S in V1 > 22mm + Strain Pattern		S in V1> 22mm+Strain Pattern
MYOCARDIAL INFARCTION				
Acute or Recent	None	All	None	All
Old	None	All	None	All
ST/T MORPHOLOGICAL				
ST elevation suggestive of Myocardial Injury	None	In 2 or more leads	None	In 2 or more leads
ST depression suggestive of Myocardial Ischaemia	None	In 2 or more leads	None	In 2 or more leads
T-wave inversion in 2 or more leads, suggestive of Ischaemia	None	All	None	All
Non-specific ST/T changes	In 2 or more leads	None	In 2 or more leads	None
PACEMAKER	None	All	None	All

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During the OL phase, 1 subject had a clinically significant ECG (Subject 3503, first-degree AV block) which was not clinically significant upon retest (**Table 102**).No subject had a clinically significant ECG in the Randomized Phase.

Table 102: Summary of Clinically Significant Changes from Baseline/Randomization in ECG (OL and Randomized ITT Population)

	OL ITT	Randomized ITT		
	LTG (N=298)	PBO (N=86)	LTG (N=87)	Total (N=173)
Clinically Significant Change, n (%)				
n	267	82	81	163
Clinically significant change from baseline/randomization	1 (<1)	0	0	0
Not a clinically significant change from baseline/randomization	266 (>99)	82 (100)	81 (100)	163 (100)

Note: Subject 185687/3503 reported a clinically significant ECG during the OL phase which was not clinically significant when retested.
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In the Randomized Phase, the incidence and types of ECG abnormalities observed were low and similar between treatment groups (**Table 103**).

Table 103: Summary of All ECG Abnormalities OL ITT Phase and Randomized Phase)

	Screening	OL	Randomized ITT-		
	LTG (N=298)	LTG (N=298)	PBO (N=86)	LTG (N=87)	Total (N=173)
SCREENING, n (%)					
Number (%) of subjects with abnormality	76 (26)	65 (22)	19 (22)	17 (20)	36 (21)
A. Rhythm, n (%)					
Any abnormality	**57 (19)**	**28 (9)**	**11 (13)**	**9 (10)**	**20 (12)**
Atrial premature complex	1 (<1)	1 (<1)	0	1 (1)	1 (<1)
Ectopic supraventricular rhythm	4 (1)	1 (<1)	1 (1)	3 (3)	4 (2)
Ectopic ventricular beats	1 (<1)	1 (<1)	0	0	0
Sinus arrhythmia	29 (10)	9 (3)	5 (6)	1 (1)	6 (3)
Sinus bradycardia	13 (4)	7 (2)	2 (2)	3 (3)	5 (3)
Sinus tachycardia	13 (4)	9 (3)	3 (3)	1 (1)	4 (2)
C. Conduction, n (%)					
Any abnormality	**35 (12)**	**34 (11)**	**7 (8)**	**8 (9)**	**15 (9)**
First degree A-V block	13 (4)	13 (4)	0	2 (2)	2 (1)
Incomplete right bundle branch block	0	1 (<1)	1 (1)	0	1 (<1)
Intra ventricular conduction delay	16 (5)	16 (5)	5 (6)	5 (6)	10 (6)
Left anterior hemiblock (synonymous to left anterior fascicular block)	1 (<1)	1 (<1)	1 (1)	0	1 (<1)
Left axis deviation	1 (<1)	1 (<1)	1 (1)	0	1 (<1)
QTcF prolongation	2 (<1)	0	0	0	0
Right bundle branch block	1 (<1)	1 (<1)	0	0	0
Short PR Interval	2 (<1)	1 (<1)	0	1 (1)	1 (<1)
D. Depolarization/Depolarization (QRTS-T), n (%)					
Any abnormality	**4 (1)**	**3 (1)**	0	0	0
Non-specific ST-T changes	4 (1)	3 (1)	0	0	0
E. Other, n (%)					
Any abnormality	**0**	**2 (<1)**	**1 (1)**	**0**	**1 (<1)**
Other abnormal rhythm	0	1 (<1)	1 (1)	0	1 (<1)
Poor R wave progression	0	1 (<1)	0	0	0
Other morphology	0	0	1 (1)	0	1 (<1)

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7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials designed to evaluate a specific safety concern were submitted in this supplemental NDA.

7.4.6 Immunogenicity

There are no immunogenicity issues related to lamotrigine.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Trial **SCA102833** was a flexible-dose study. Therefore, no specific assessments for dose dependency of adverse events were done.

7.5.2 Time Dependency for Adverse Events

No specific assessments for dose dependency of adverse events were done in this randomized withdrawal study (Trial **SCA102833**).

7.5.3 Drug-Demographic Interactions

The sponsor provided an extensive analysis of drug-associated adverse events by age subgroup. This is discussed in detail in Sections 7.3 and 7.4 above.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

As described in current prescribing information for Lamictal, there was no evidence of carcinogenicity in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to 2 years at maximum tolerated doses10 to 15 mg/kg/day. See Section 13.1 of current Lamictal labeling for further details.

7.6.2 Human Reproduction and Pregnancy Data

As described in the current prescribing information for Lamictal, LTG is a pregnancy category C medication. No new or unexpected information about the effects of LTG on pregnancy was obtained during Trial **SCA102833**.

During the OL Phase of Trial **SCA102833**, one 17 year-old white subject (Subject 050373) became pregnant. She received lamotrigine at an increasing total daily dose ranging from 25 mg to 250 mg daily from November 10, 2008 to February 26, 2009. The subject received blinded trial medication from February 27, 2009. She was randomized to lamotrigine. At an unknown date after the start of investigational product, the subject was reported to be pregnant. Treatment with investigational product was discontinued

on October 1, 2009 and the subject was withdrawn from the trial. The subject's last menstrual period was reported to be (b) (6) and her estimated date of delivery was (b) (6). She did not respond to efforts to follow-up on the pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Trial **SCA102833** is intended to fulfill the requirement for a pediatric study under PREA for the maintenance treatment of Bipolar I Disorder in pediatric patients ages 10 to 17 years. A consultation with the Pediatric and Maternal Health Staff has been obtained and is pending at the time of this writing.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Overdoses involving quantities up to 15 g have been reported for LTG, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay. The current prescribing information provides up to date information on overdose and overdose management.

In **SCA102833**, during the Randomized Phase, 1 subject (Subject 000503) who received PBO was admitted to the hospital and diagnosed as having committed a severe intentional drug overdose. It was estimated that he had taken 80 tablets of sodium valproate, 10 tablets of aripiprazole, and 24 tablets of PBO.

Drug Abuse

The abuse and dependence potential of LTG have not been evaluated in human studies (see Lamictal Prescribing Information).

Withdrawal and Rebound

Withdrawal and rebound were assessed during Trial **SCA102833** by monitoring AEs in the OL and Double-blind Taper Phases. Few AEs were reported during the Taper Phases. In the OL Taper Phase, 14 (40%) subjects reported AEs. AEs reported in ≥5% of subjects included headache (20%), somnolence (6%), and suicidal ideation (6%). All other AEs were reported in ≤5% of subjects.

In the Double-Blind Taper Phase, 18 (34%) subjects in the LTG group and 14 (25%) in the PBO group reported AEs. Headache was the only AE reported in ≥5% (8% in the LTG group and 7% in the PBO group). All other AEs were reported in ≤5% of subjects. One (3%) SAE was reported in the OL Taper Phase (bipolar disorder) and 2 (3%) subjects reported SAEs in the Double-blind Taper Phase (infectious mononucleosis,

urinary tract infection, and suicidal ideation). Both of the subjects in the Double-blind Taper Phase were in the PBO group.

No seizures were reported in the taper phases of Trial **SCA102833**, however as with other AEDs, Lamictal should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in adult subjects with BPD, 2 subjects experienced seizures shortly after abrupt withdrawal of Lamictal; however, there were confounding factors that may have contributed to the occurrence of seizures in these BPD subjects. Unless safety concerns require a more rapid withdrawal, the dose of Lamictal should be tapered over a period of at least 2 weeks (approximately 50% reduction per week) (see Lamictal Prescribing Information).

7.7 Additional Submissions / Safety Issues

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Trial **SCA102833** did not evaluate the effects on ability to drive or operate machinery or impairment of mental ability.

Patients should be advised that Lamictal may cause dizziness, somnolence, and other symptoms and signs of CNS depression. Accordingly, they should be advised to neither drive a car nor operate complex machinery until they have gained sufficient experience with Lamictal to gauge whether or not it adversely affects their mental and/or motor performance (see Lamictal Prescribing Information).

Adult BPD and Pediatric Efficacy trials

Per previous agreement with the FDA, data from the 2 pivotal trials in adults with bipolar disorder (BPD) (Trials **SCAB2003** and **SCAB2006**) and the 2 controlled trials of adjunctive treatment with Lamictal in pediatric patients with epilepsy (**UK123** and **US40**) are presented in this submission for comparison with the safety data in Trial **SCA102833**.

Safety data were combined for the two adult BPD trials (**SCAB2003** and **SCAB2006**). Data from **SCA102833** were not combined with the data from adult trials for the following reasons:

- The study populations differed (children and adolescents vs. adult), and
- The study designs differed with respect to monotherapy vs. adjunctive therapy, stabilization criteria prior to randomization.

While safety information From Trial **SCA102833** is presented for the entire trial population (age 10-17, discussed above), discussion and comparison with adult BPD trials and pediatric epilepsy trials are focused on the 13-17 year-old population (b) (4)

(b) (4)

. Trial **SCA102833** data were presented by the sponsor for the overall population (10-17 years of age) and also predefined age subgroups (10-12 years and 13-17 years). These groups allowed analysis of LTG efficacy in prepubertal (younger group) vs. postpubertal (older group), and allowed comparison to the prior adult trials as it is generally accepted that the presentation in adolescents (13-17 years old) is similar to adults, according to the sponsor. Because the safety data is focused on the 13-17 year old subgroup from **SCA102833**, this subgroup is presented side-by-side with the adult BPD studies and the pediatric epilepsy studies.

Adult BPD Trials

Trials **SCAB2003** and **SCAB2006** were multicenter, double-blind, double-dummy, parallel-group, placebo- and lithium-controlled, randomized trials evaluating the safety and efficacy of LTG in the long-term prevention of relapse and recurrence of depression and/or mania in adult subjects with BPD (Type I) (see **Section 6.2 Adult Bipolar Disease (BPD) Trials SCAB2003 and SCAB2006).**

Pediatric Epilepsy Trials (UK123 and US 40)

UK123, "Lamotrigine as Add-on Therapy in Patients with a Clinical Diagnosis of Lennox-Gastault syndrome (Severe Generalized Epilepsy of Childhood Onset)," was the pivotal trial supporting approval of Lamictal as adjunctive therapy of the generalized seizures of Lennox-Gastault syndrome in subjects 3 to 25 years of age (**NDA 20241/S-002** and **NDA 20764**; approved August 1998).

US 40, "A Multicenter, Double-blind, Placebo-controlled, Parallel-design Evaluation of Lamictal for Add-on Treatment of Partial Seizures in Pediatric Patients," was the pivotal trial supporting the use of Lamictal as adjunctive treatment of partial seizures in pediatric subjects 2 to 16 years of age (**NDA 20(b) (4)241/S-008** and **NDA 20764/S-002**; approved January 2003).

The pediatric epilepsy trials had the largest percentage of subjects in the 6-12 and ≥13 year old age groups, as shown in **Table 104** below.

Table 104: Demographic Characteristics (Age and Gender) for Adjunct Epilepsy Studies (Studies US 40 and UK 123)

	N	Total n (%)	<2 yrs. n (%)	2-5 yrs. n (%)	6-12 yrs. n (%)	≥13 yrs. n (%)
Males						
PBO	171	92 (54)	0	23 (25)	56 (61)	13 (14)
LTG	168	93 (55)	0	28 (30)	48 (52)	17 (18)
Females						
PBO	171	79 (46)	1 (1)	26 (33)	42 (53)	10 (13)
LTG	168	75 (45)	0	19 (25)	47 (63)	9 (12)

Source: Summary of Clinical Safety; Table 10, page 17

Comparison of Safety Profile: SCA102833 13-17 year old Subgroup, Adult BPD, and Pediatric Epilepsy

Adverse Events:

In the OL Phase, the incidence of AEs, was higher in Trial **SCA102833** (83%) compared with the Adult BPD Trials (75%), as shown in **Table 105** below. However, in general, the types and incidences of specific AEs were similar between groups with the exception of headache, nausea, abdominal pain upper, irritability, and suicidal ideation which were reported with a higher incidence in Trial **SCA102833**.

Table 105: Most Common AEs (≥5% in Trial SCA102833) (SCA102833, 13-17 year old Subgroup ITT Population, Adult BPD Trials, Safety Population, OL Phase)

	Number (%) of Subjects	
Adverse Event	SCS102833 13-17 yrs (N=181)	Adult BPD Studies (SCAB2003 and SCAB2006) (N=1305)
Any Adverse Event	**151 (83)**	**974 (75)**
Headache	64 (35)	333 (26)
Nausea	32 (18)	162 (12)
Abdominal pain upper	30 (17)	63 (5)
Nasopharyngitis	18 (10)	52 (4)
Oropharyngeal pain	18 (10)	0
Insomnia	18 (10)	109 (8)
Dizziness	17 (9)	126 (10)
Diarrhea	16 (9)	113 (9)
Vomiting	16 (9)	68 (5)
Cough	15 (8)	35 (3)
Fatigue	12 (7)	70 (5)
Suicidal ideation	11 (6)	15 (1)
Irritability	11 (6)	0
Sinusitis	11 (6)	35 (3)
Dyspepsia	9 (5)	66 (5)
Upper respiratory tract infection	9 (5)	0
Decreased appetite	9 (5)	0

Note: AEs are ordered in decreasing incidence in the LTG group of Trial SCA102833
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In the Randomized Phase, the overall incidence of AEs in Trial **SCA102833** was similar to that in the Adult BPD trials across treatment groups, as shown in **Table 106** below. Within treatment groups, the types and incidence of AEs was similar between Trial S**CA102833** and the adult BPD trials. The incidence of AEs in the Pediatric Epilepsy trials was generally lower than for the 13-17 year old subgroup in **SCA102833** and the Adult Bipolar trials with the exception of vomiting and pyrexia where the incidence was higher in the Pediatric Epilepsy trials.

Table 106: Most Common AEs (≥5% in Trial SCA102833) (SCA102833, 13-17 year old Subgroup ITT Population, Adult BPD and Pediatric Epilepsy Trials, Safety Population, Randomized Phase)

	SCA102833 13-17 yr		Adult BPD Studies (SCAB2003 and SCAB2006)		Adjunctive Pediatric Epilepsy Studies US 40 and UK 123[b]	
Adverse Event	PBO (N=53)	LTG (N=54)	PBO (N=190)	LTG (N=227)	PBO (N=171)	LTG (N=168)
Any Event, n (%)	**37 (70)**	**39 (72)**	**137 (72)**	**166 (73)**	NR	NR
Headache	11 (21)	8 (15)	36 (19)	42 (19)	19 (11)	18 (11)
Influenza	2 (4)	5 (9)	17 (9)	19 (8)	10 (6)	12 (7)
Oropharyngeal pain	2 (4)	5 (9)	0	0	0	0
Nasal congestion	4 (8)	4 (7)	7 (4)	17 (7)	0	0
Insomnia	4 (8)	4 (7)	12 (6)	22 (10)	0	0
Agitation	0	3 (6)	5 (3)	8(4)	0	0
Anxiety	0	3 (6)	5 (3)	6 (3)	0	0
Vomiting	0	3 (6)	4 (2)	11 (5)	25 (15)	31 (19)
Irritability	11 (21)	2 (4)	0	0	0	0
Nasopharyngitis	3 (6)	2 (4)	6 (3)	12 (5)	0	0
Upper respiratory tract infection	4 (8)	2 (4)	0	0	0	0
All mania[a]	4 (8)	2 (4)	13 (7)	11 (5)	0	0
-Mania	4 (8)	2 (4)	11 (6)	9 (4)	0	0
-Bipolar I disorder	2 (4)	1 (2)	0	0	0	0
-Bipolar disorder	2 (4)	1 (2)	0	0	0	0
-Mixed manic depression	0	0	3 (2)	9 (4)	0	0
Dizziness	4 (8)	1 (2)	17 (9)	17 (7)	3 (2)	20 (12)
Pyrexia	3 (6)	0	1 (<1)	8 (4)	24 (14)	25 (15)

Note: AEs are ordered in decreasing incidence in the LTG group of Trial SCA102833
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Serious Adverse Events:

In the OL Phase, few subjects reported SAEs in Trial **SCA102833**. In the 13-17 year old subgroup, a total of 11 (6%) subjects reported a total of 15 SAEs, as shown in **Table 107** below. The types and incidence of SAEs between Trial **SCA102833** and the Adult BPD Trials was similar.

It should be noted that the adult BPD trials were completed prior to the use of the Columbia Suicide Severity Rating Scale (C-SSRS) to prospectively monitor for suicidal behavior and ideation. Thus, these comparisons should be interpreted with caution.

Table 107: Summary of SAEs in the OL Phase in SCA102833, 13-17 year old Subgroup (SCA102833 13-17 year old Subgroup ITT Population, Adult BPD Trials, Safety Population)

Adverse Event	SCA102833 LTG 13-17 yrs (N=181)	Adult BPD Studies (SCAB2003 and SCAB2006) (N=1305)
Any Event, n (%)	**11 (6)**	**115 (9)**
Suicidal ideation	4 (2)	12 (<1))
All Mania	3 (2)	37 (3)
Mania	2 (1)	32 (2)
Bipolar I disorder	1 (<1)	0
Hypomania	0	5 (<1)
Mixed manic-depressive episode	0	2 (<1)
Irritability	1 (<1)	0
Anxiety	1 (<1)	1 (<1)
Impulsive behavior	1 (<1)	0
Intentional self-injury	1 (<1)	2 (<1)
Agitation	1 (<1)	1 (<1)

Note: AEs are ordered in decreasing incidence in the LTG group of Trial SCA102833
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In the Randomized Phase of Trial **SCA102833**, no LTG-treated subject in the 13-17 year old subgroup reported SAEs, as shown in **Table 108** below. There were SAEs of mania reported in both treatment groups in the Adult BPD trials, and 1 (2%) in the PBO group of **SCA102833**. There were no apparent differences in SAEs, but there were few AEs overall in this category.

Table 108: Summary of SAEs Reported in the Randomized Phase in SCA102833, 13-17 year old Subgroup (SCA102833, Randomized ITT Population, Adult BPD and Pediatric Epilepsy Trials, Safety Population)

	SCA102833 13-17 yrs		Adult BPD Studies (SCAB2003 and SCAB2006)		Adjunctive Pediatric Epilepsy Studies[b]	
Adverse Event	PBO N=53	LTG N=54	PBO N=190	LTG N=227	PBO N=171	LTG N=168
Any event, n (%)	**2 (4)**	**0**	**26 (14)**	**25 (11)**	**8 (5)**	**14 (8)**
Intentional overdose	1 (2)	0	0	0	0	0
All Mania[a]	1 (2)	0	12 (6)	11 (5)	0	0
-Bipolar I disorder	1 (2)	0	0	0	0	0
-Mania	0	0	10 (5)	9 (4)	0	0
-Mixed manic-depressive episode	0	0	3 (2)	2 (<1)	0	0

Note: AEs are ordered in decreasing incidence in the LTG group of Trial SCA102833
Electronically copied and reproduced from sponsor's submission: Summary of Clinical Safety; Table 27, page 32.

AEs Leading to Trial Withdrawal:

In the OL Phase, 16 (9%) subjects in Trial **SCA102833** and 180 (14%) subjects in the Adult BPD trials reported AEs leading to withdrawal, as shown in **Table 109** below. Of the AEs leading to withdrawal in Trial **SCA102833**, all were reported at a similar incidence to the Adult BPD trials, with the exception of All Rash and rash which were reported at a higher incidence in the Adult BPD trials.

Table 109: Summary of AEs Leading to Withdrawal (SCA102833 13-17 year old Subgroup ITT Population, Adult BPD Trials, Safety Population, OL Phase)

Adverse Event	SCA102833 13-17 yrs N=181	Adult BPD Studies (SCAB2003 and SCAB2006) N=1305
Any Event, n (%)	**16 (9)**	**180 (14)**
Suicidal ideation	5 (3)	7 (<1)
All Mania[a]	3 (2)	25 (2)
-Mania	2 (1)	20 (2)
-Bipolar I disorder	1 (<1)	0
-Hypomania	0	4 (<1)
-Mixed manic-depressive episode	0	2 (<1)
All Rash[b]	3 (2)	60 (5)
-Rash	2 (1)	56 (4)
-Dermatitis allergic	1 (<1)	0
-Maculopapular rash	0	3 (<1)
-Erythema multiforme	0	1 (<1)
-Steven's Johnson Syndrome	0	1 (<1)
-Urticaria	0	1 (<1)
Agitation	2 (<1)	2 (<1)
Intentional self-injury	2 (<1)	0
Irritability	2 (<1)	0
Anger	1 (<1)	0
Anxiety	1 (<1)	5 (<1)
Dermatitis	1 (<1)	0
Neutropenia	1 (<1)	0

Note: AEs are ordered in decreasing incidence in the LTG group of Trial SCA102833
Electronically copied and reproduced from sponsor's submission: Summary of Clinical Safety; Table 31, page 37.

In the Randomized Phase, a higher percentage of subjects reported AEs leading to withdrawal in Trial **SCA102833** than in the Adult BPD or Pediatric Epilepsy trials, as shown in **Table 110** below. Of the AEs leading to withdrawal reported in Trial **SCA102833**, none were reported in the Pediatric Epilepsy trials. Of the AEs leading to withdrawal reported in Trial **SCA102833**, these were reported at a similar incidence to those in the Adult BPD trials although in the LTG groups, a higher incidence of agitation and All Mania were reported in Trial **SCA102833**.

Table 110: Summary of AEs Leading to Premature Discontinuation (SCA102833 ITT Population, Adult BPD and Pediatric Epilepsy Trials, Safety Population, Randomized Phase)

Adverse Event	SCA102833		Adult BPD Studies (SCAB2003 and SCAB2006)		Adjunctive Pediatric Epilepsy Studies US 40 and UK 123[b]	
	PBO N=53	LTG N=54	PBO N=190	LTG N=227	PBO N=171	LTG N=168
Any Event, n (%)	**15 (28)**	**11 (20)**	**30 (16)**	**29 (13)**	**5 (3)**	**7 (4)**
Agitation	0	3 (6)	2 (1)	1 (<1)	0	0
Irritability	11 (21)	2 (4)	0	0	0	0
All Mania[a]	4 (8)	2 (4)	5 (3)	4 (2)	0	0
-Mania	2 (4)	1 (2)	5 (3)	4 (2)	0	0
-Bipolar I disorder	2 (4)	1 (2)	0	0	0	0
Aggression	1 (2)	1 (2)	1 (<1)	0	0	0
Anxiety	0	1 (2)	0	0	0	0
Panic attack	0	1 (2)	0	0	0	0
Self injurious behavior	0	1 (2)	0	0	0	0
Suicide attempt	0	1 (2)	1 (<1)	0	0	0
Blood thyroid stimulating hormone abnormal	0	1 (2)	0	0	0	0
Depression	1 (2)	0	3 (2)	3 (1)	0	0
Depressed mood	1 (2)	0	1 (<1)	0	0	0
Elevated mood	1 (2)	0	0	0	0	0
Insomnia	1 (2)	0	2 (1)	1 (<1)	0	0
Mood swings	1 (2)	0	1 (<1)	3 (1)	0	0
Anger	1 (2)	0	0)	0	0	0
Intentional overdose	1 (2)	0	0	0	0	0

Note: AEs are ordered in decreasing incidence in the LTG group of Trial SCA102833
Note: Although 12 subjects reported AEs leading to withdrawal in pediatric epilepsy trials, none were in common to those reported in SCA102833.
Electronically copied and reproduced from sponsor's submission: Summary of Clinical Safety; Table 32, page 39.

There are no apparent differences in AEs leading to withdrawal, but there were few AEs overall in this category.

8 Postmarket Experience

Based on IMS (Intercontinental Medical Statistics) Health data, cumulative postmarketing exposure to LTG worldwide is estimated to be (b) (4) patient years (to 30 September 2013). For the USA, the estimated cumulative number of patient years is (b) (4). The algorithm used to derive post-marketing exposure data from IMS assumes an average daily dose of (b) (4) mg LTG.

LTG is not approved for the treatment of BPD in patients aged below 18 years of age in any country. Post-marketing reports relating to use of LTG for the treatment of BPD in

the pediatric population (10 to 17 years of age) are therefore limited to use in an unapproved population i.e. 'off label'. A search of the GSK worldwide safety database retrieved 692 cases where LAMICTAL was reported to have been prescribed for the treatment of BPD for patients aged 10 to 17 years of age, with the majority (81.6%) of the cases reported from the US. Of the 692 cases, 264 were not reported to be receiving additional therapy for the treatment of bipolar disorder (BPD monotherapy), whilst in the remaining 428 cases the patient was reported to be receiving one or more medication routinely prescribed for BPD (combination therapy). Two hundred and forty nine cases were classified as serious.

Of the five fatal cases reported, three reported hypersensitivity reactions such as rash or multi-organ failure, whilst the remaining two described completed suicide.

A high-level comparison of the adverse events reported for LTG monotherapy and LTG combination therapy (i.e. LTG used in combination with one or more medication(s) used to treat BPD) did not highlight any major differences. The system organ classes (SOC) containing the most frequently reported events (>5% of the total number of reports) were: Skin and subcutaneous tissue disorders, General disorders and administration site conditions, Gastrointestinal disorders, Psychiatric disorders, and Nervous system disorders for both monotherapy and combination therapy. For the combination therapy group, the Investigations SOC also reported >5% of the events, whereas the monotherapy group did not. Overall, with the exception of the Investigations SOC, there were no notable differences in the number of events reported in each SOC for the two groups (allowing for the difference in the total number of events reported: 659 for monotherapy and 1,542 for combination therapy).

Events in the psychiatric disorders SOC are particularly relevant for the bipolar disorder indication. Fifty-five serious cases reported events in this SOC including two with a fatal outcome. For both the monotherapy and combination therapy groups, no single event was reported at a notably high frequency. After allowing for the differences in the total number of events auditory and visual hallucinations, bipolar disorder, psychotic disorder and tic appear to be more frequently reported with monotherapy, whilst anxiety and insomnia appear to be more frequently reported with combination therapy.

As could be reasonably expected from the current knowledge on the safety profile of LTG, the skin and subcutaneous tissue disorders SOC contained the majority of events: 32.5% and 28.2% of the total number of events for the monotherapy and combination therapy group, respectively. One hundred and forty seven serious cases reported events in this SOC including 3 cases with a fatal outcome. After allowing for the differences in the total number of events reported for this SOC in each group, no notable differences in the reporting frequency of any event was observed.

In general, the reported events were consistent with the current product label, and also consistent with the safety profile observed in the approved adult BPD indication. The

analysis also indicated that there were no notable differences between the use of LTG as monotherapy or in combination with other medications used to treat BPD. However, many of the reported events are also consistent with the product information for the concomitant medication(s).

9 Appendices

9.1 Literature Review/References

A comprehensive review of the published literature was performed, with the safety issues reported in these publications generally being currently described in the prescribing information for LTG and/or under current periodic review. None of the information presented in these publications results in a change to the overall risk: benefit of LTG. The review confirms the known safety profile of LTG and the current product labeling accurately reflects this profile.

9.2 Labeling Recommendations

Sponsor's Proposed Labeling:

(b) (4)

(b) (4)

Under **Section 8.4 Pediatric Use**, the sponsor proposes the following changes (sponsor's revisions in track changes):

Epilepsy: LAMICTAL is indicated for adjunctive therapy in patients 2 years of age for partial seizures, the generalized seizures of Lennox-Gestault syndrome, and primary generalized tonic-clonic seizures.

Safety and efficacy of LAMICTAL, used as adjunctive treatment for partial seizures, were not demonstrated in a small, randomized, double-blind, placebo-controlled, withdrawal (b) (4) in very young pediatric patients (aged 1 to 24 months (b) (4)). LAMICTAL was associated with an increased risk for infectious adverse reactions (LAMICTAL 37%, placebo 5%), and respiratory adverse reactions (LAMICTAL 26%, placebo 5%). Infectious adverse reactions included bronchiolitis, bronchitis, ear infection, eye infection, otitis external, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included nasal congestion, cough, and apnea.

(b) (4)

Bipolar Disorder: Safety and efficacy of LAMICTAL for the treatment of bipolar disorder were not (b) (4) in a (b) (4)

aged 10 to 17 years. In the randomized phase of the trial, (b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Recommendations:

(b) (4)

A brief description of study design and efficacy and safety results from Trial **SCA102833** should be included in **Section 8.4 Pediatric Use**. This section should include results for the overall population (aged 10-17 years) (b) (4) . I propose the following (my revisions and additions to current Lamictal labeling are in track changes):

Epilepsy: LAMICTAL is indicated for adjunctive therapy in patients 2 years of age for partial seizures, the generalized seizures of Lennox-Gestault syndrome, and primary generalized tonic-clonic seizures.

Safety and efficacy of LAMICTAL, used as adjunctive treatment for partial seizures, were not demonstrated in a small, randomized, double-blind, placebo-controlled, withdrawal study in very young pediatric patients (aged 1 to 24 months (b) (4)). LAMICTAL was associated with an increased risk for infectious adverse reactions (LAMICTAL 37%, placebo 5%), and respiratory adverse reactions (LAMICTAL 26%, placebo 5%). Infectious adverse reactions included bronchiolitis, bronchitis, ear

infection, eye infection, otitis external, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included nasal congestion, cough, and apnea.

(b) (4)

Bipolar Disorder: Safety and efficacy of LAMICTAL for the treatment of bipolar disorder were not demonstrated in a double-blind, placebo-controlled trial that evaluated children and adolescents aged 10 to 17 years. The trial enrolled subjects with a current

(b) (4)

In the randomized phase of the trial, adverse reactions which occurred in at least 5% of subjects taking LAMICTAL (N=87) and were numerically more common compared to subjects talking placebo (N=86) were influenza (Lamictal 8%, placebo 2%), oropharyngeal pain (Lamictal 8%, placebo 2%), insomnia (Lamictal 7%, placebo 6%), cough (Lamictal 7%, placebo 5%), nasopharyngitis (Lamictal 6%, placebo 5%), vomiting (Lamictal 6%, placebo 2%), contact dermatitis (Lamictal 5%, placebo 2%), upper abdominal pain (Lamictal 5%, placebo 1%), and suicidal ideation (Lamictal 5%, placebo 0%).

At the time of this writing, labeling recommendations are under internal discussion. In addition, consultation with the Division of Pediatric and Maternal Health for input regarding **Section 8.4** (**Pediatric Use**) of labeling has been requested and is pending.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting is planned for this application. (b) (4)

the Division concluded that an Advisory Committee would not be helpful at this time because no new safety concerns have been identified and, from a statistical standpoint, efficacy of Lamictal in the

maintenance treatment of Bipolar Disorder has not been demonstrated for the intended population.

Francis E. Becker, M.D., F.A.C.P.
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 22251, 20764, and 20241
HFD 130
M Mathis
T Farchione
L Kempf
S Sagoo

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANCIS E BECKER
02/12/2015

LUCAS P KEMPF
03/09/2015